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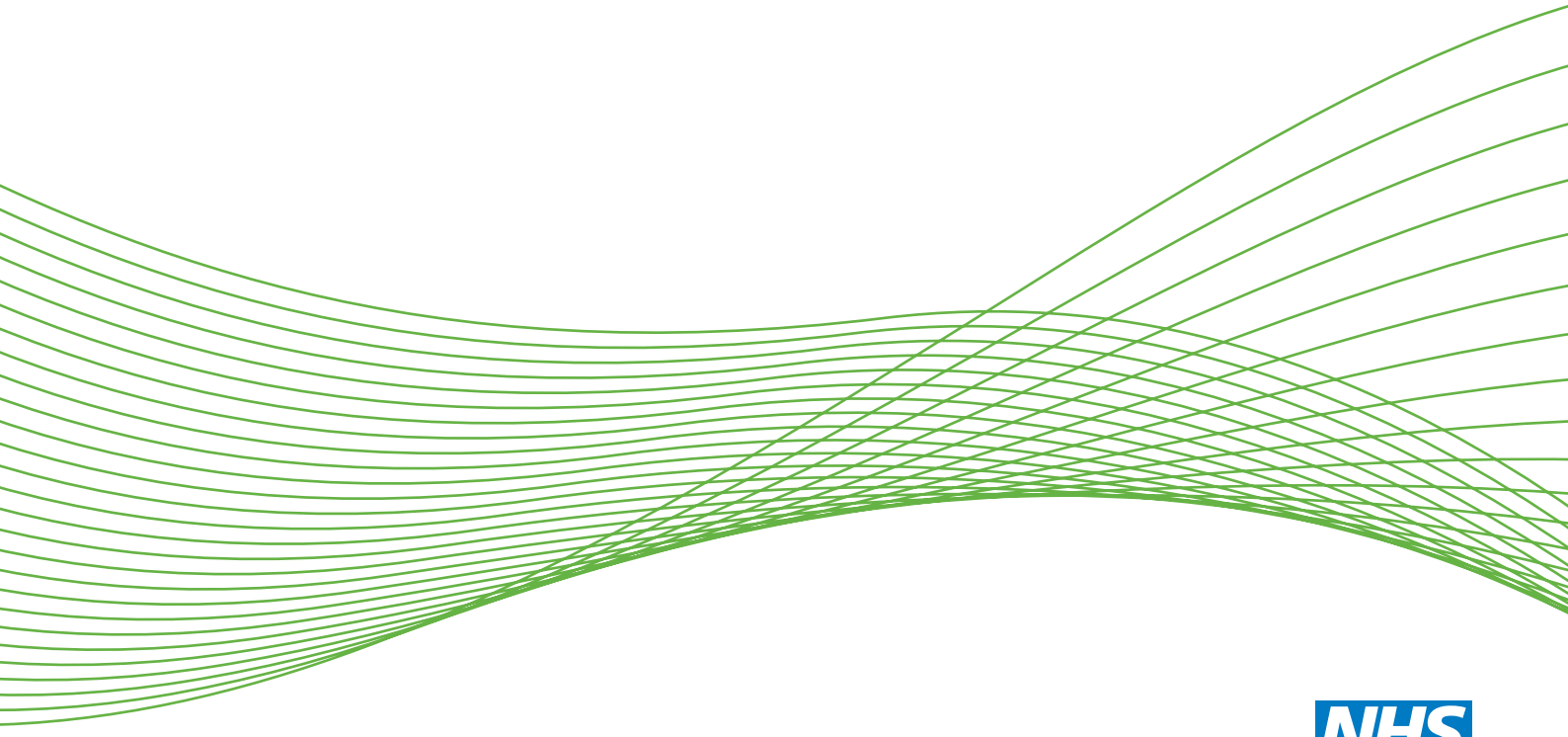

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Abstract

TRAPEZE: a randomised controlled trial of the clinical effectiveness and cost-effectiveness of chemotherapy with zoledronic acid, strontium-89, or both, in men with bony metastatic castration-refractory prostate cancer

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Background: Bony metastatic castration-refractory prostate cancer is associated with a poor prognosis and high morbidity. TRAPEZE was a two-by-two factorial randomised controlled trial of zoledronic acid (ZA) and strontium-89 (Sr-89), each combined with docetaxel. All have palliative benefits, are used to control bone symptoms and are used with docetaxel to prolong survival. ZA, approved on the basis of reducing skeletal-related events (SREs), is commonly combined with docetaxel in practice, although evidence of efficacy and cost-effectiveness is lacking. Sr-89, approved for controlling metastatic pain and reducing need for subsequent bone treatments, is generally palliatively used in patients unfit for chemotherapy. Phase II analysis confirmed the safety and feasibility of combining these agents. TRAPEZE aimed to determine the clinical effectiveness and cost-effectiveness of each agent.

Methods: Patients were randomised to receive six cycles of docetaxel plus prednisolone: alone, with ZA, with a single Sr-89 dose after cycle 6, or with both. Primary outcomes were clinical progression-free survival (CPFS: time to pain progression, SRE or death) and cost-effectiveness. Secondary outcomes were SRE-free interval (SREFI), total SREs, overall survival (OS) and quality of life (QoL). Log-rank test and Cox regression modelling were used to determine clinical effectiveness. Cost-effectiveness was assessed from the NHS perspective and expressed as cost per additional quality-adjusted life-year (QALY). An additional analysis was carried out for ZA to reflect the availability of generic ZA.

Results: Patients: 757 randomised (median age 68.7 years; Eastern Cooperative Oncology Group scale score 0, 40%; 1, 52%; 2, 8%; prior radiotherapy, 45%); median prostate-specific antigen 143.78 ng/ml (interquartile range 50.8–353.9 ng/ml). Stratified log-rank analysis of CPFS was statistically non-significant for either agent (Sr-89, $p = 0.11$; ZA, $p = 0.45$). Cox regression analysis adjusted for stratification variables showed CPFS benefit for Sr-89 [hazard ratio (HR) 0.845, 95% confidence interval (CI) 0.72 to 0.99; $p = 0.036$] and confirmed no effect of ZA ($p = 0.46$). ZA showed a significant SREFI effect (HR 0.76; 95% CI 0.63 to 0.93; $p = 0.008$). Neither agent affected OS (Sr-89, $p = 0.74$; ZA, $p = 0.91$), but both increased total cost (vs. no ZA and no Sr-89, respectively); decreased post-trial therapies partly offset costs [net difference: Sr-89 £1341; proprietary ZA (Zometa®, East Hanover, NJ, USA) £1319; generic ZA £251]. QoL was maintained in all trial arms; Sr-89 (0.08 additional QALYs) and ZA (0.03 additional QALYs) showed slight improvements. The resulting incremental cost-effectiveness ratio (ICER) for Sr-89 was £16,590, with £42,047 per QALY for Zometa and £8005 per QALY for generic ZA.

Conclusion: Strontium-89 improved CPFS, but not OS. ZA did not improve CPFS or OS but significantly improved SREFI, mostly post progression, suggesting a role as post-chemotherapy maintenance therapy. QoL was well maintained in all treatment arms, with differing patterns of care resulting from the effects of Sr-89 on time to progression and ZA on SREFI and total SREs. The addition of Sr-89 resulted in additional cost and a small positive increase in QALYs, with an ICER below the £20,000 ceiling per QALY. The additional costs and small positive QALY changes in favour of ZA resulted in ICERs of £42,047 (Zometa) and £8005 for the generic alternative; thus, generic ZA represents a cost-effective option. Additional analyses on the basis of data from the Hospital Episode Statistics data set would allow corroborating the findings of this study. Further research into the use of ZA (and other bone-targeting therapies) with newer prostate cancer therapies would be desirable.

Study registration: Current Controlled Trials ISRCTN12808747.

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List of abbreviations

AE	adverse event
BCa	bias corrected and accelerated
BNF	*British National Formulary*
CEAC	cost-effectiveness acceptability curve
CI	confidence interval
CPFS	clinical progression-free survival
CRCTU	Cancer Research Clinical Trials Unit
CRF	case report form
CRPC	castration-refractory prostate cancer
CT	computed tomography
DMC	Data Monitoring Committee
DXA	dual-energy X-ray absorption scan
ECOG	Eastern Cooperative Oncology Group
eMIT	electronic market information tool
EQ-5D	European Quality of Life 5-Dimensions
FACT-P	Functional Assessment of Cancer Therapy – Prostate
HR	hazard ratio
HRPC	hormone-refractory prostate cancer
HRQoL	health-related quality of life
ICER	incremental cost-effectiveness ratio
IQR	interquartile range
mCRPC	metastatic castration-refractory prostate cancer
NICE	National Institute for Health and Care Excellence
OS	overall survival
PPFI	pain progression-free interval
PSA	prostate-specific antigen
QALY	quality-adjusted life-year
QoL	quality of life
SAE	serious adverse event
SCC	spinal cord compression
Sr-89	strontium-89
SRE	skeletal-related event
SREFI	skeletal-related event-free interval
TSC	Trial Steering Committee
VAS	visual analogue scale
ZA	zoledronic acid

Plain English summary

TRAPEZE evaluated the use of two bone-targeting therapies, strontium-89 (Sr-89) and zoledronic acid (ZA), in men receiving docetaxel chemotherapy for relapsing prostate cancer involving the skeleton. Bony disease can cause pain, fractures and other serious complications. Docetaxel has been shown to increase survival and improve quality of life (QoL) in this setting. Intravenous ZA has been shown to reduce skeletal complications in prostate cancer, but is not recommended for general use because of doubts over its cost-effectiveness. Sr-89 is a radioactive drug taken up by bone cancer deposits and is recommended by the National Institute for Health and Care Excellence when chemotherapy is unsuitable.

TRAPEZE showed that adding Sr-89 to docetaxel delayed deterioration by around a month, but did not result in any improvement in overall survival. Adding ZA did not delay deterioration but did reduce subsequent serious bone complications by around one-third, with a 50% reduction in the most serious events such as fracture and spinal cord compression. QoL was well maintained. Both drugs increased treatment costs but decreased post-trial therapy costs because of delayed deterioration and, for ZA, decreased surgery and radiotherapy for bone complications.

Incremental costs per quality-adjusted life-year (QALY) for branded ZA and Sr-89 were calculated at £42,047 and £16,590, respectively. Sr-89 net acquisition was £1341 with modest gains in QoL and cost per QALY gained, a measure of the effectiveness of drug treatments. For ZA, net acquisition was £1319, but this cost was reduced to £251 by using the generic drug. The cost per QALY for the generic drug fell to £8005, making ZA both cost-effective and clinically effective as a therapy.

Scientific summary

Prostate cancer is a major health problem worldwide and accounts for nearly one-fifth of all newly diagnosed male cancers. In the UK, approximately 35,000 men are diagnosed with prostate cancer each year, and in 2008 almost 10,000 men died from the disease. The disease is mostly one of older age, but significant numbers of men of working age will develop the disease.

Although prostate cancer most often presents as local disease, a significant proportion of patients progress despite initial treatment with ablative surgery or radiotherapy, often in combination with hormonal therapy. A minority of patients present with de novo metastatic disease.

Hormone therapy has been the mainstay of treatment for relapsed prostate cancer since the seminal studies of Huggins and Hodges, published in 1941, demonstrating substantial and prolonged remissions from prostate cancer with the use of either surgical castration or oestrogen therapy (Huggins C, Hodges CV. Studies on prostatic cancer. I. The effect of castration, of estrogen and androgen injection on serum phosphatases in metastatic carcinoma of the prostate. *Cancer Res* 1941;**1**:293–7). Responses to hormone therapy typically last 18–24 months, depending on disease stage. This period after failure of initial androgen deprivation therapy was previously known as hormone-refractory prostate cancer. However, with the recognition that relapsing tumours remain dependent on androgen receptor-mediated pathways and the recent licensing in relapsing disease of abiraterone, a steroid synthesis inhibitor, and enzalutamide, an androgen receptor-targeting agent, the term castration-refractory prostate cancer (CRPC) is increasingly used and will be the preferred term in this report.

Chemotherapy with docetaxel is also a mainstay of therapy for metastatic castration-refractory prostate cancer (mCRPC) following two landmark trials published in the *New England Journal of Medicine* in 2004 (Tannock IF, de Wit R, Berry WR, Horti J, Pluzanska A, Chi KN, *et al.* Docetaxel plus prednisolone or mitoxantrone plus prednisolone for advanced prostate cancer. *N Engl J Med* 2004;**351**:1502–12; and Petrylak DP, Tangen CM, Hussain MH, Lara PN, Jr., Jones JA, Taplin ME, *et al.* Docetaxel and estramustine compared with mitoxantrone and prednisolone for advanced refractory prostate cancer. *N Engl J Med* 2004;**351**:1513–20). Both trials showed improved palliative outcomes compared with mitoxantrone and, very importantly, an overall survival advantage for 3-weekly docetaxel and the docetaxel–estramustine combination with hazard ratios (HRs) of 0.76 and 0.8, respectively. On the basis of these trials, a 3-weekly schedule of docetaxel plus prednisolone for up to 10 cycles has emerged as the standard of care for mCRPC/CRPC and was approved by the National Institute for Health and Care Excellence (NICE) for this purpose in 2006. A number of post-chemotherapy treatments have been licensed on the basis of improvements in overall survival since 2010, including cabazitaxel, abiraterone and enzalutamide.

In patients with mCRPC, one of the most common sites of spread is bone, and bone metastases are a major cause of morbidity in men with CRPC. Bone morbidity is often quantified in clinical trials via a composite end point termed the skeletal-related events (SREs):

- pathological fracture
- spinal cord compression
- radiotherapy to bone
- hypercalcaemia
- change in anticancer treatment to treat bone pain.

Bisphosphonates inhibit bone catabolism by reducing the numbers of functioning osteoclasts and have been used to manage bone metastases. Zoledronic acid (ZA), but not some older bisphosphonates, also arrests cell proliferation, induces apoptosis and inhibits the growth factor stimulation of cultured prostate cancer cells. In trials in relapsing mCRPC, ZA reduced the time to SREs, as well as the frequency of subsequent SREs. The ZA licensing trials have proved very controversial, as the fracture end point was assessed by regular skeletal survey

with blinded radiological assessment. Hence, there is significant doubt as to whether many of the small fractures detected were precursors of a subsequent real 'clinical' SRE or radiological features of no significance. ZA is not currently recommended for use in the UK by NICE because of doubts as to its cost-effectiveness.

Radioisotopes have been used to palliate bone pain for over 20 years. A variety of radioisotopes are available; the most commonly used during the trial recruitment era were strontium-89 (Sr-89) and samarium-153. Both accumulate selectively in bone metastases compared with non-involved bone. There is some evidence that Sr-89 may reduce overall health-care costs compared with standard methods of delivering radiotherapy. There are a number of previous studies of combined use of chemotherapy with radioisotopes. Of particular note, Tu *et al.* combined combination chemotherapy with Sr-89 in a small randomised trial with promising results, suggesting a survival advantage in chemotherapy responders allocated to Sr-89 (Tu SM, Millikan RE, Mengistu B, Delpassand ES, Amato RJ, Pagliaro LC, *et al.* Bone-targeted therpay for advanced androgen-independent carcinoma of the prostate: a randomised phase II trial. *Lancet* 2001;**357**:336–41).

This study sought to assess whether or not the addition of Sr-89 or ZA offers a significant benefit in combination with docetaxel and prednisolone in CRPC metastatic to bone. The primary research questions of the study are as follows:

- Does upfront use of bone-targeting agents with chemotherapy improve clinical outcomes?
- Is it more cost-effective to prevent bone complications or to treat them as they arise?

Design

This is a randomised controlled Phase III trial with a two-by-two factorial design which proceeded seamlessly from a randomised controlled four-arm Phase II trial. The Phase II trial objectives were to compare the four trial arms with respect to feasibility, tolerability and safety. The Phase III trial objectives were to assess treatments with respect to efficacy within a two-by-two factorial design framework; that is, the trial compared ZA with no ZA (stratified for Sr-89 use) and Sr-89 with no Sr-89 (stratified for ZA use). The primary outcome measures for the Phase III trial were both clinical progression-free survival (CPFS) (defined in relation to bone) and cost-effectiveness.

The Phase II end points of feasibility, tolerability and safety are subsumed within Phase III of the trial as secondary outcomes. The funding for Phase II was not provided by the Health Technology Assessment (HTA) programme of the National Institute for Health Research, and the preliminary Phase II analysis formed the basis of the HTA programme application for funding. We do not propose to present detailed analysis of the Phase II subset of patients in this report, as feasibility is confirmed by the successful completion of the Phase III trial.

Setting

UK oncology departments.

Participants

Men with CRPC metastatic to bone who are eligible for treatment with first-line chemotherapy.

Interventions

Arm A: docetaxel 75-mg/m^2 intravenously 3-weekly for up to 10 cycles.

Arm B: docetaxel as above plus ZA 4-mg intravenously 3-weekly during chemotherapy, then 4-weekly until disease progression.

Arm C: docetaxel as above for six cycles, Sr-89 150 MBq, then further docetaxel up to total of 10 cycles.

Arm D: docetaxel plus both Sr-89 and ZA as above.

Main outcome measures

Phase II

Primary: feasibility, tolerability and safety in terms of cycles of docetaxel and ZA and Sr-89, cycle delays, dose reductions and toxicity.

Secondary: CPFS, SRE-free survival, pain progression-free interval, overall survival (OS), costs, quality of life (QoL).

Phase III

Primary: CPFS, costs and cost-effectiveness.

Secondary: SRE-free survival, pain progression-free interval, OS.

All phases: additional substudies not part of this report

Changes in bone mineral density, biological profiling for prognostic and predictive indicators, prostate-specific antigen-related outcomes, patient-reported pain-related outcomes.

Data sources (if applicable)

Data were collected by research staff in the treating hospitals on standard case report forms.

Statistical methods

The trial examined the clinical efficacy of adding bone-targeting treatment to standard chemotherapy. Assuming that clinically worthwhile differences were seen, the costs associated with the extra therapy were analysed and used to estimate the clinical cost-effectiveness of the trial interventions. If no significant differences were seen, or if the trial interventions worsened outcomes, then the health economic analysis was clearly considered redundant.

The clinical analysis was conducted under a two-by-two factorial design; as such, we can consider the results of Sr-89 and ZA comparisons separately. In addition, in the interests of clarity, we shall also present the results of the health economic evaluation separately.

Clinical analysis

Strontium-89 comparison

In the control arm, median time to CPFS was 8.8 months from randomisation. This increased to 9.8 months with the addition of Sr-89 after cycle 6 [HR for benefit of 0.85 on multivariable analysis, 95% confidence interval (CI) 0.77 to 0.99; $p = 0.036$]. As some patients did not complete six cycles of chemotherapy, they did not get to the point of receiving Sr-89; we therefore did a second analysis restricted to those patients completing six cycles of chemotherapy. Resetting the time to progression from the sixth chemotherapy cycle makes the time to progression 4.3 months and 5.3 months, respectively, to give a HR for benefit of 0.8 on multivariable analysis (95% CI 0.66 to 0.97; $p = 0.024$). There was no improvement in overall survival (HR 0.97, 95% CI 0.82 to 1.15).

Zoledronic acid comparison

In the ZA arm, median control time to CPFS was, again, 8.8 months from randomisation. This also increased to 9.7 months, but the difference was not statistically significant (HR 0.94, 95% CI 0.81 to 1.10; $p = 0.457$). There was also no improvement in overall survival (HR 1.01, 95% CI 0.85 to 1.20). ZA did, however, show a highly significant effect on skeletal-related event-free interval (HR 0.76, 95% CI 0.63 to 0.93; $p = 0.008$). There was no improvement in overall survival (HR 1.01, 95% CI 0.85 to 1.20).

Economic evaluation

Strontium-89 comparison

The most prominent difference in mean patient costs between the Sr-89 and no Sr-89 groups is a result of the cost of the Sr-89 radioisotope itself. Apart from higher cost of Sr-89, the Sr-89 group was associated with a greater cost for docetaxel and ZA given as protocol treatments, higher cost of cabazitaxel and docetaxel provided as concomitant medications and increased cost because of surgery. On the other hand, this group was associated with a lower use of radiotherapies, abiraterone, ZA and Sr-89 as concomitant medications, as well as fewer inpatient days, outpatient appointments and GP visits. This resulted in a mean cost difference of £1341 (95% bias-corrected and accelerated bootstrap method 95% CI –£66 to £2748). In terms of quality-adjusted life-years (QALYs), patients receiving Sr-89 presented a slightly greater number (0.08) of QALYs than those not receiving Sr-89. The point estimate incremental cost-effectiveness ratio (ICER) for Sr-89 compared with that for no Sr-89 was calculated at £16,590 per additional QALY. For prices of an administration of Sr-89 up to £2120, the ICER for Sr-89 remains below the £20,000 per QALY mark.

Zoledronic acid comparison

The difference in mean patient costs between the ZA and no ZA groups was, to a great extent, because of the use of ZA (mean difference £2197). Excluding the use of ZA, patients in the ZA group presented lower resource use and costs than those in the no ZA group. In particular, there were significant differences in the use of radiotherapy and surgery for skeletal-related problems. If ZA is considered as a branded product with an acquisition cost of £174 for a 4-mg dose, the difference in total cost between ZA and no ZA is £1319. On the other hand, taking into account the availability of generic ZA at a significantly lower cost reduced the difference in total cost to £251. In terms of QALYs, ZA appeared to be slightly more effective than no ZA, resulting in a gain of 0.03 QALYs. The additional costs and the small but positive change in QALYs in favour of ZA resulted in ICERs of £8005 for the generic-based price and £42,047 for the proprietary product. Whether or not the addition of ZA to chemotherapy represents a cost-effective use of resources depends largely on the acquisition cost of a 4-mg dose of ZA. If this acquisition cost is up to £98, which is the most likely scenario because of the availability of generic ZA, the ICER for ZA is below £20,000 per QALY and, thus, this option is cost-effective at this ceiling ratio.

Conclusions

In terms of impact on the primary outcome measure of bony progression-free survival, the Sr-89 arm was positive but with a relatively modest absolute benefit and no improvement in OS. In contrast, there was no evidence that the ZA arm was of benefit for the primary outcome measure and OS, but there was evidence of a benefit in terms of impact on SRE-free interval and total SRE numbers. On the basis of the positive effects seen, undertaking the health economic evaluation for both agents was considered worthwhile.

The impact of the trial therapies on the primary outcome measure of cost-effectiveness is interesting. Although associated with relatively modest benefits, Sr-89 met the cost-to-QALY ratio of less than £20,000 that is considered to represent effective use of NHS resources. In contrast, ZA had more tangible clinical benefits in the form of a substantial reduction in SREs and increased time to first SRE. These did not translate into sizeable QoL benefits, as QoL was maintained by increased use of other therapies, particularly surgery and radiotherapy. Hence, patients traded attendance for a predictable preventative therapy for attendances for needs-driven palliative therapies. The ICER for proprietary ZA is high, at £42,047, largely because of the lack of impact on QoL. As noted above, taking into account the recent availability of generic ZA at low prices, ZA resulted in an additional cost of £251 and an ICER of £8005. Given the pressure on NHS emergency resources, trusts may consider this cost to be good value for money, as it converts unpredictable events such as fracture or spinal cord compression into predictable outpatient workload. Additional analyses on the basis of data from the Hospital Episode Statistics data set would allow corroborating the findings of this study. Further research into the use of ZA (and other bone-targeting therapies) with newer prostate cancer therapies would be desirable.

Study registration

This trial is registered as ISRCTN12808747.

Funding

Funding for this study was provided by the Health Technology Assessment programme of the National Institute for Health Research.

Chapter 1 Introduction

Background

Prostate cancer

Prostate cancer is a major worldwide health problem which accounts for nearly one-fifth of all newly diagnosed male cancers. In the UK, approximately 35,000 men are diagnosed with prostate cancer each year, and in 2008 almost 10,000 men died from the disease.[1] The disease is mostly one of older age, but significant numbers of men of working age will develop the disease. *Figure 1* summarises the age distribution of incident cases and deaths.

Although adenocarcinoma of the prostate most often presents as local (stage T1 or T2) disease, in which the malignancy is confined to the prostate, a significant proportion of patients progress despite initial treatment with ablative surgery or radiotherapy, often in combination with hormonal therapy. A minority of patients present with de novo metastatic disease. *Figure 2* summarises the treatment options across the disease spectrum.

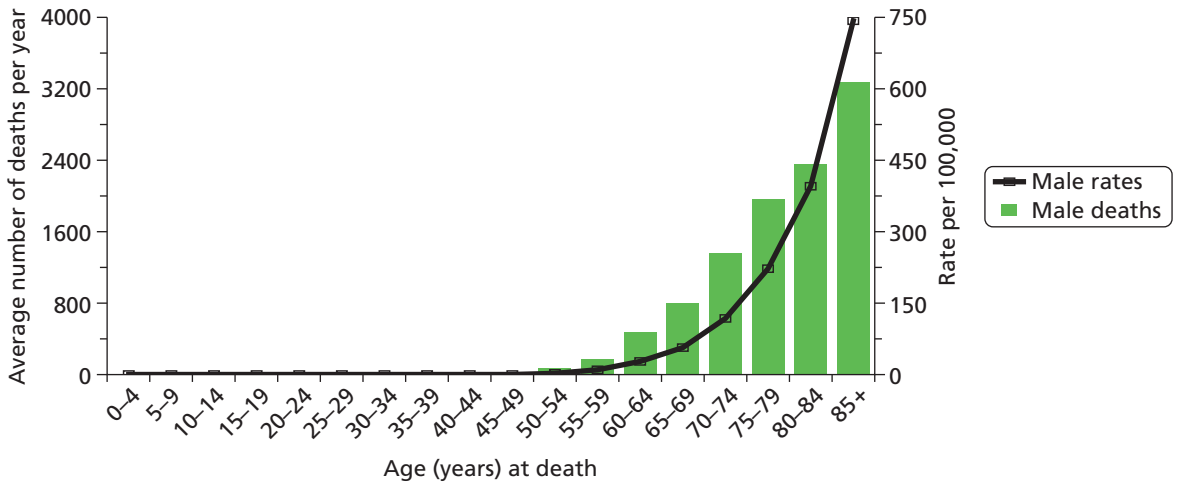


FIGURE 1 Prostate cancer incidence and mortality in the UK.[2–4]

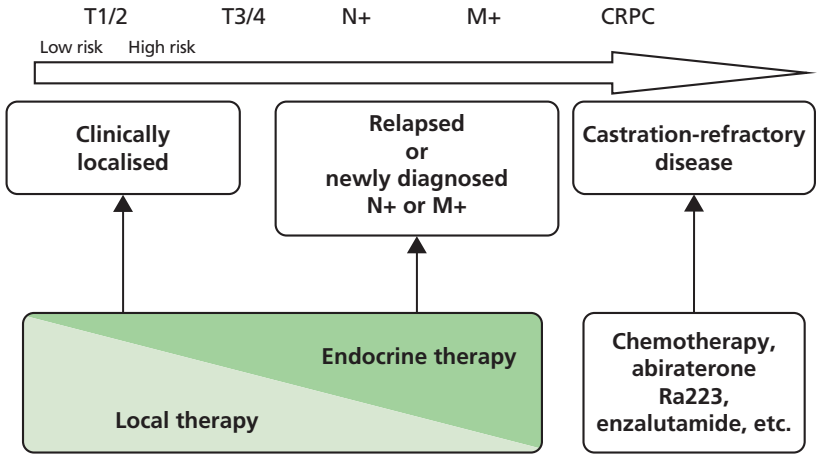


FIGURE 2 Prostate cancer treatment paradigm. Cancer has spread to the pelvic lymph nodes (N+) or to lymph nodes, organs, or bones distant from the prostate (M+). CRPC, castration-refractory prostate cancer; Ra223, Radium-223.

Hormone therapy

A hormone (from the Greek ὁρμή, meaning 'impetus') is a chemical released by a cell in one part of the body to affect cells in other parts of the organism. Cells respond to a hormone when they express a specific receptor for that hormone. The hormone binds to the receptor protein, resulting in the activation of a signal transduction mechanism that ultimately leads to cell type-specific responses. Hormone therapies can thus work on a number of points in this pathway and there are examples of all of these in prostate cancer, which are summarised in *Table 1*.

Hormone therapy has been a mainstay of prostate cancer since the seminal studies of Huggins and Hodges,[5] published in 1941, demonstrating substantial and prolonged remissions from prostate cancer with the use of either surgical castration or oestrogen therapy. Diethylstilboestrol is the first example of a successful drug treatment for advanced cancer, and, while now supplanted in this role, it remains in use 70 years later. As is now well known, while responses to hormone therapy may be dramatic, with durations running into many years, they are rarely curative and typically last 18–24 months depending on disease stage. This period after failure of initial androgen deprivation therapy has been known by many terms over the years, including androgen-independent prostate cancer and castration-refractory prostate cancer (CRPC). However, with the recognition that relapsing tumours remain dependent on androgen receptor-mediated pathways and the licensing in relapsing disease of abiraterone,[6–8] a steroid synthesis inhibitor, and enzalutamide,[9] an androgen receptor-targeting agent, the term castration-refractory prostate cancer is increasingly used. This term is, however, unpopular with patient groups and, while accurate, may yet also be supplanted if anyone can think of a term with less pejorative overtones.

Broadly speaking, there are two routes into long-term hormone therapy: via localised disease, radical therapy and relapse, and de novo advanced disease (*Figure 3*).

TABLE 1 Hormone therapy targets

Target	Example in prostate cancer therapy
Block synthesis of regulator of hormone	Gonadotropin-releasing hormone analogues and antagonists, e.g. goserelin, leuprorelin, triptorelin
Block binding of secreted hormone to receptor	Bicalutamide, enzalutamide, cyproterone acetate
Block post-receptor effects	Enzalutamide
Block synthesis of hormone	Cyp17 inhibitors, e.g. abiraterone
Add alternative hormones to alter environment	Diethylstilboestrol, dexamethasone

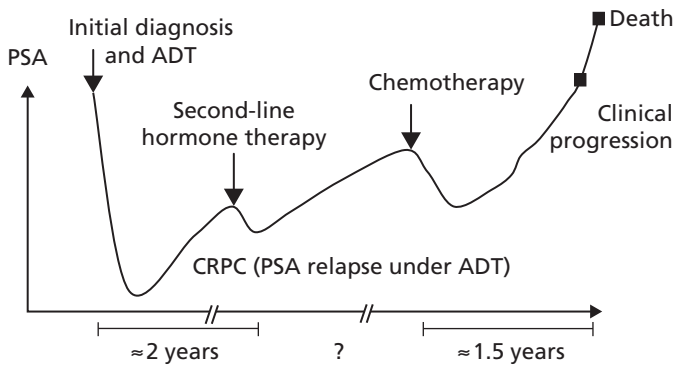


FIGURE 3 Pathways to advanced disease. Natural history for metastatic patients. ADT, androgen deprivation therapy; PSA, prostate-specific antigen.

Figure 3 shows disease burden expressed via the prostate-specific antigen (PSA) level on the vertical axis. For most purposes, however, PSA does equate with disease burden. In particular, in late-stage disease managed with non-hormonal therapies the relationship is not that close and PSA is not recognised as a surrogate end point for clinical trials. In early hormone-sensitive disease, the concordance between PSA changes and clinical ones is close. One consequence of the use of the PSA test is that managment tends to be PSA-driven rather than clinically-driven. In the case of patients relapsing after failed local therapy, clinicians are faced with a rising PSA but often no radiological evidence of disease for many years – termed a biochemical relapse. Patients in this situation will often be started on hormone therapy many years before any clinical consequences of relapse. Randomised trials in this setting have shown that intermittent therapy is as good as continuous therapy and probably should be regarded as the standard of care.

Management of metastatic disease

Initial management of men with locally advanced or metastatic prostate cancer is some form of androgen deprivation therapy. This will generally control disease for 1–3 years, following which progressive clinical failure will ensue – CRPC. In patients with metastatic CRPC (mCRPC), one of the most common sites of spread is bone. The development of bone metastasis, and the associated pain, results in a high level of mobility problems, leading to a loss of functional independence in men, and is a major cause of mortality [bone marrow failure, pathological fractures, spinal cord compression (SCC) and other bone-related complications]. Bone morbidity is often quantified in clinical trials via a composite end point termed the skeletal-related events (SREs). The elements that make up this end point are summarised as:

- pathological fracture
- SCC
- radiotherapy to bone
- hypercalcaemia
- change in anticancer treatment to treat bone pain.

The reduction in the frequency or severity of SREs that any particular patient experiences during the individual disease pathway may provide additional health-related quality-of-life (HRQoL) benefits. The true benefit in terms of HRQoL is not yet completely known, although recent data from clinical trials have begun to show the HRQoL benefits of bisphosphonates.[10,11] In addition to the potential quality-of-life (QoL) benefits, patients may also gain actual survival benefit from either mono or combination therapy. Although bisphosphonates therapy and/or chemotherapy may be considered as central to the treatment of patients with bone metastases, other therapies such as radioisotopes are available and are widely used for patients with mCRPC.

Chemotherapy

For many years chemotherapy was considered too toxic to be of value in men with advanced prostate cancer. There were a number of reasons for this, including later diagnosis in the pre-PSA era, difficulty in assessing responses and problems in managing toxicity, such as nausea and vomiting. The advent of PSA-driven diagnosis and management, while remaining controversial in terms of use as a screening test, has undoubtedly resulted in a strong trend to earlier diagnosis now dating back several decades. This in turn has meant that men are diagnosed younger with advanced disease. Secondly, the use of PSA monitoring post-primary treatment has meant that men relapsing after failed radical therapy are picked up early and so, when mCRPC does develop, treatment can be instigated when men remain fit enough to cope with it. Definitive proof of benefit from palliative chemotherapy came from a landmark National Cancer Institute of Canada trial led by Ian Tannock from Toronto. The trial compared prednisone alone with prednisolone plus mitoxantrone given 3-weekly for up to 10 cycles. This relatively small study of 161 patients published in 1996 set out to compare palliative end points rather than survival-based ones.[12]

A palliative response was observed in 23 out of 80 patients who received mitoxantrone plus prednisone, compared with 10 out of 81 patients who received prednisone alone. In an additional seven patients in each group, analgesic medication was reduced without an increase in pain. The duration of palliation was longer in patients who received chemotherapy (with a median of 43 weeks to symptom worsening) than in those treated with prednisone alone (median of 18 weeks to symptom worsening). There was significant crossover from the prednisone arm to the chemotherapy arm and no difference in overall survival. Thus, this study clearly established the principle that chemotherapy could provide palliative benefit but did not show a survival benefit. Subsequent mitoxantrone trials produced similar results, although the crossover between the chemotherapy and no-chemotherapy arms means that, essentially, it is not known whether or not chemotherapy with this agent produces a survival benefit.

In the late 1990s, a variety of agents started to be evaluated in what was then called hormone-refractory prostate cancer (HRPC). Docetaxel emerged as the lead candidate for evaluation in large phase trials, and two landmark studies were published in the *New England Journal of Medicine* in 2004.[13,14] One trial, the TAX327 study,[13] compared weekly or 3-weekly docetaxel with the Tannock mitoxantrone regimen. The second trial (SWOG 9916[14]) compared a combination of docetaxel and estramustine with the same control arm. Both trials showed improved palliative outcomes compared with mitoxantrone and, very importantly, an overall survival (OS) advantage for 3-weekly docetaxel and the docetaxel–estramustine combination with hazard ratios (HRs) of 0.76 and 0.8, respectively, despite significant crossover to docetaxel in the mitoxantrone arms of both studies. All patients in both trials received prednisone as per the original Tannock paper. These trials confirmed unequivocally that chemotherapy could both prolong survival and give worthwhile palliation without undue toxicity. They also established that docetaxel is a superior agent to mitoxantrone. On the basis of these trials, a 3-weekly schedule of docetaxel plus prednisolone for up to 10 cycles has emerged as the standard of care for mCRPC and was approved by the National Institute for Health and Care Excellence (NICE) for this purpose in 2006 (*Figure 4*).

A number of agents have been studied in the second-line chemotherapy setting. Of these, to date only cabazitaxel has shown a survival advantage and obtained a licence. The key trial, TROPIC, compared cabazitaxel with mitoxantrone given on the standard Tannock trial schedule and showed an improvement in median survival from 12.7 to 15.1 months.[16] Cabazitaxel was licensed in 2010 ahead of abiraterone, which obtained a licence in 2011 in the same post-docetaxel setting. As both drugs improve survival,

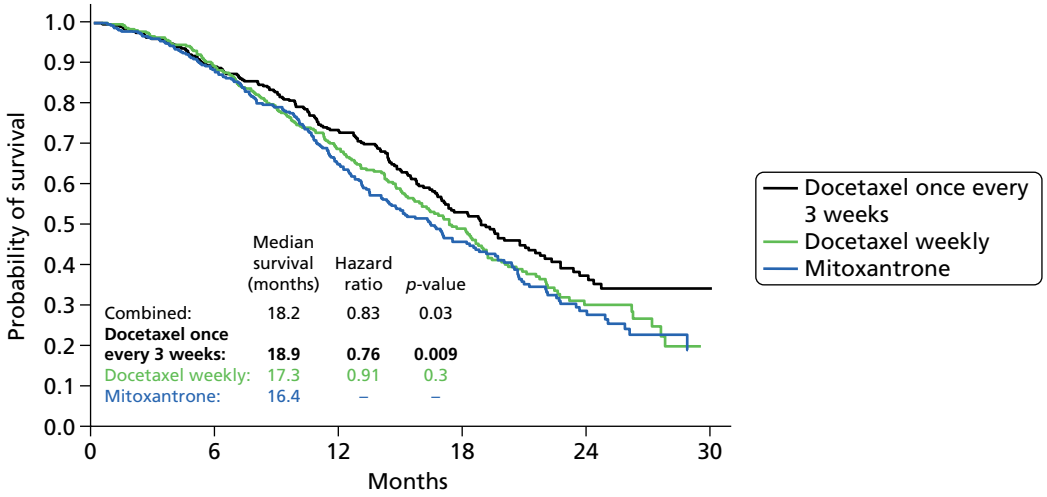


FIGURE 4 Comparison of estimated probability of overall survival of mitoxantrone and docetaxel for CRPC.[15]

although they have completely different modes of action, there is clearly an unresolved issue over choice and sequencing (or indeed combination) of agents. The position has now been further complicated by the licensing of enzalutamide post chemotherapy based on the AFFIRM trial,[9] plus the extension of the abiraterone licence to chemo-naive patients.[6] The licence for enzalutamide was also expanded to cover pre-chemotherapy patients following the PREVAIL trial.[17]

Additionally, the recent publication of the results of the ALSYMPCA trial of radium-223[18] demonstrated both improved OS and reduced skeletal complications with six injections, one every 28 days, of radioisotope compared with placebo.[18] How chemotherapy should best be integrated with other therapeutic options for patients with bone metastasis is at present not defined.

Bisphosphonates

Bisphosphonates inhibit bone catabolism by reducing the numbers of functioning osteoclasts and have been used to manage bone metastases. Zoledronic acid (ZA), but not some older bisphosphonates, also arrest cell proliferation, induce apoptosis, and inhibit the growth factor stimulation of cultured prostate cancer cells.[14] In trials in relapsing mCRPC, ZA reduced the time to SRE as well as the frequency of subsequent SREs.[19,20] The ZA licensing trials[19,20] have proved very controversial, as the fracture end point was assessed by regular skeletal survey with blinded radiological assessment. Hence, there is significant doubt as to whether many of the small fractures detected were precursors of a subsequent real 'clinical' SRE or radiological features of no significance. ZA is not currently recommended for use in the UK by NICE because of doubts as to its cost-effectiveness.

Radioisotopes have been used to palliate bone pain for over 20 years. A variety of radioisotopes are available; the most commonly used during the trial recruitment era were strontium-89 (Sr-89)[21,22] and samarium-153.[23] Both accumulate selectively in bone metastases compared with non-involved bone. There is some evidence that Sr-89 may reduce overall health-care costs compared with standard methods of delivering radiotherapy.[24] There are a number of previous studies of combined use of chemotherapy with radioisotopes. Of particular note, Tu *et al.*[25] combined combination chemotherapy with Sr-89 in a small randomised trial with promising results suggesting a survival advantage in chemotherapy responders allocated to Sr-89.

Since the publication of the MRC PR05 study,[26,27] more potent bisphosphonates have been evaluated in mCRPC. The most widely studied has been zoledronate, which has a 40- to 850-fold higher potency than clodronate in pre-clinical models of bone resorption.[28] It has also been shown to be more effective than pamidronate (90 mg) in controlling malignant hypercalcaemia[29,30] In addition, zoledronate has demonstrated direct anticancer activity, including inhibition of proliferation of breast cancer and prostate cancer cells in vitro.[31,32]

In prostate cancer trials in relapsing mCRPC, ZA reduced the time to SREs as well as the frequency of subsequent SREs.[19,20] However, it is clear from looking at the components that make up the SREs that these vary hugely in clinical significance and, in addition, are to a degree subjective. In particular, the ZA licensing trials[19,20] have proved very controversial as the fracture end point was assessed by regular skeletal survey with blinded radiological assessment. As such there is significant doubt about whether many of the small fractures detected were precursors of a subsequent real 'clinical' SRE or radiological features of no significance. The subsequent trials comparing ZA with denusomab[33] used the same methodology and so can be subject to the same criticism. As a result, neither agent is recommended for use in the UK by NICE. The impact of ZA on SREs is illustrated in *Figure 5*; the bisphosphonate showing decreases in skeletal complications in both lytic and blastic lesions in a comparison with pamidonate.[20]

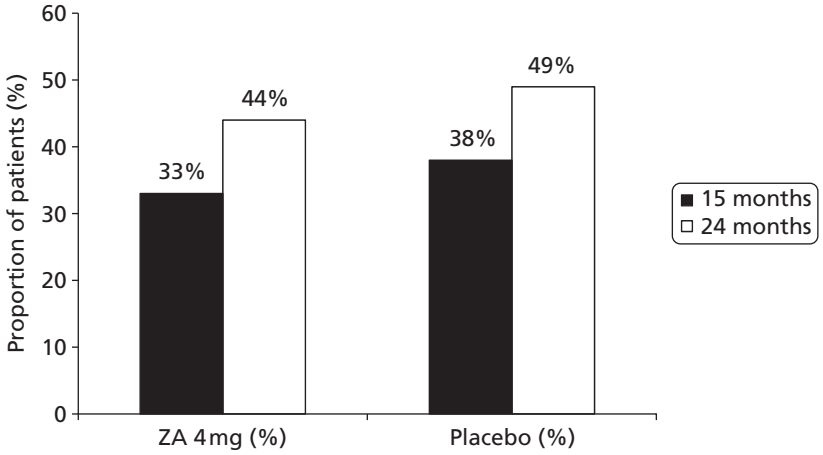


FIGURE 5 Proportion of patients with SREs, demonstrating reduction with ZA.

In vitro evidence suggests synergistic killing of breast and prostate cancer cells when combined with chemotherapy.[32] Furthermore, ZA was licensed in the 'pre-docetaxel' era; hence, whatever the merits of SRE prevention, the role of zoledronate in the chemotherapy era was effectively undefined. It was therefore logical to evaluate docetaxel with ZA in men with mCRPC affecting bone. In view of the controversy over the SRE as an end point, we did not undertake routine skeletal evaluations as in the zoledronate and denosumab licensing trials but collected data only on 'clinical' SREs; that is, those reported by the patient or diagnosed on the basis of symptoms such as those from SCC. We combined this clinically orientated approach to the SRE with a health economic assessment of the impact of the various trial interventions, the intention being that, if the clinical utility of combination therapy were confirmed, we should be able to produce robust estimates of the cost-effectiveness at the same time.

Radioisotopes

A variety of radioisotopes are available, the most commonly used during the trial recruitment era being Sr-89 and samarium-153. Both accumulate selectively in bone metastases compared with uptake rates in non-involved bone. Sr-89, a bone-seeking radionuclide, is a pure β-emitter with a half-life of 50 days, has a high uptake in osteoblastic metastases, and remains in tumour sites for up to 100 days. Sr-89 provides pain relief in up to 80% of patients, and complete freedom from pain in approximately 10%, for periods that can exceed 3 months.[21,34] In a randomised controlled Phase III trial, the combination of Sr-89 injection and external beam radiotherapy improved pain relief, delayed disease progression and enhanced some QoL measures compared with external beam radiotherapy alone.[21] However, another Phase III randomised controlled trial has suggested that, in some patients, systemic Sr-89 may be inferior to local-field radiotherapy in terms of survival (7.2 months vs. 11.0 months; $p = 0.0457$).[22] The selection of patients has a significant impact on outcome, response and duration of response to radionuclide therapy, as bone pain palliation is reduced in those who have widespread metastatic disease or a short life expectancy.[35–38] Consequently, the use of radionuclides appears to be optimal at an early stage in disease management. However, their efficacy is reduced or lost with repeated use, and overtreatment can also lead to irreversible pancytopenia. As noted above (see *Bisphosphonates*), there is some evidence that Sr-89 may reduce overall health-care costs compared with standard methods of delivering radiotherapy.[39]

There are a number of previous studies of combined use of chemotherapy with radioisotopes. Tu *et al.* combined combination chemotherapy with Sr-89 in a small randomised trial with promising results suggesting a survival advantage in chemotherapy responders allocated to Sr-89.[25] More recently, Fizazi *et al.*,[40] Tu *et al.*[41] and Morris *et al.*[42] have combined docetaxel with samarium-153 in Phase I/II trials, confirming safety for the combination. No published randomised trials have addressed the safety or efficacy of docetaxel with either Sr-89 or samarium-53.

As new treatments have appeared for CRPC, these treatments have been less frequently used. However, recent data with a new radioisotope radium-223 seem set to change this picture. Like Sr-89, radium-223 is a calcium mimetic. Recently completed placebo-controlled Phase III trials in symptomatic CRPC patients showed a prolongation of survival and also a delay and reduction in symptomatic (as opposed to radiological) SREs.[18] Levels of adverse reactions reported in the trial were low. The agent was licensed in 2013 and is an important new therapeutic option for men with CRPC, especially as the trial included men both pre and post chemotherapy, as well as those deemed unfit to ever receive chemotherapy.

Osteoporosis

Patients eligible for the study are at risk of osteoporosis in view of their previous therapy (androgen deprivation, possible steroid exposure, age) as well as from some on-study therapies (steroids, docetaxel). Osteoporosis was therefore considered in the causality of any SRE. A bone density substudy formed part of this trial.

Chapter 2 Methods

Trial design

This was originally a four-arm randomised controlled Phase II trial, which proceeded seamlessly to a Phase III trial. In order to increase efficiency and reduce the trial duration, the Phase III design was switched from a four-arm comparison to a two-by-two factorial design. The end points changed as the trial progressed from Phase II to Phase III, as summarised in *Table 2*.

The Phase II objectives were to compare the four trial arms with respect to feasibility, tolerability and safety. The Phase III objectives were to assess treatments with respect to efficacy within a two-by-two factorial design framework; that is, the trial compared ZA versus no ZA (stratified for Sr-89 use) and Sr-89 versus no Sr-89 (stratified for ZA use). The Phase III trial had dual primary end points of effect of each treatment on time to bony disease progression and cost and cost-effectiveness.

During the chemotherapy treatment period, participants were assessed at 3-weekly intervals. Irrespective of treatment arm, all patients were assessed at the end of the sixth cycle of chemotherapy to ensure their fitness to receive Sr-89.

Phase II participants ceased primary trial treatment after cycle 6 of Sr-89 administration, where relevant. Clinicians were encouraged to give further docetaxel off-trial up to a total of 10 cycles in keeping with NICE guidance, where appropriate. In order to streamline data collection, cycles 7 to 10 of docetaxel were designated as trial therapy for Phase III of the study.

TABLE 2 Summary of study end points

Phase	Primary	Secondary	Tertiary
II	• Feasibility, tolerability and safety in terms of cycles of docetaxel and ZA and Sr-89, cycle delays, dose reductions and toxicity	• CPFS • SRE-free survival • Pain progression-free interval • OS • Costs • QoL	• Changes in bone mineral density (substudy) • Biological profiling for prognostic and predictive indicators (substudy) • PSA-related outcomes • Patient-reported pain-related outcomes
III	• Clinical progression-free survival • Costs and cost-effectiveness	• SRE-free interval • Pain progression-free survival • OS • QoL • Toxicity	• Changes in bone mineral density (substudy) • Biological profiling for prognostic and predictive indicators (substudy) • PSA-related outcomes • Patient-reported pain-related outcomes

CPFS, clinical progression-free survival.

Participants

Male patients over the age of 18 years were recruited into the trial. The trial recruited sufficient patients to ensure that at least 618 participants reached the primary end points. The entry criteria primarily included proven mCRPC, with one or more of progressive sclerotic bone metastases, progression of measurable malignant lesions or elevated and rising PSA levels on blood analysis. Consenting participants had to have had an Eastern Cooperative Oncology Group (ECOG) scale score of up to 2, be fit enough to receive trial treatment and have adequate haematological, renal and hepatic function.

Exclusion criteria included prior chemotherapy or radionuclide therapy for CRPC, prior radiotherapy to more than 25% of bone marrow or whole-pelvic irradiation, prior bisphosphonate therapy within 2 months of trial entry, other malignant disease within the previous 5 years (excluding adequately treated basal cell carcinoma), known brain metastases, symptomatic peripheral neuropathy of National Institutes of Health National Cancer Institute's Common Terminology for the Criteria for Adverse Events grade 2 or more, concurrent participation in any other clinical trial involving an investigational therapeutic compound or treatment with other investigational compound within the 30 days prior to trial entry.

Owing to the nature of the treatments under investigation, this was not a blinded trial for patients or caregivers.

Interventions

Arm A: control – docetaxel plus prednisolone

Docetaxel 75 mg/m^2 (up to a maximum dose of 165 mg) was administered intravenously at 3-weekly intervals (21 days). Participants also received oral prednisolone 10 mg daily throughout trial treatment or until disease progression or associated treatment toxicity.

Trial chemotherapy ceased after cycle 6 for Phase II participants but continued for up to 10 cycles for Phase III participants, ceasing for pain or tumour disease progression, or other cause decided by the treating clinician or patient choice. As noted above (see *Trial design*) patients could receive further chemotherapy off-trial in keeping with NICE guidance.

Arm B: docetaxel, prednisolone plus zoledronic acid

Docetaxel and prednisolone were administered as per the control arm. ZA was administered intravenously after completion of docetaxel administration at a dose of 4 mg, subject to pre-treatment creatinine clearance being greater than 60 ml/minute; creatinine clearance of < 60 ml/minute would incrementally reduce the dose given, as detailed in section 6.1.3 of the protocol (see *Appendix 1*). Following the completion of chemotherapy, participants received continuing ZA at 4-weekly intervals, as clinically indicated, until pain or tumour disease progression or withdrawal. It was recommended that patients treated with ZA also receive vitamin D and calcium supplements throughout treatment.

Arm C: docetaxel, prednisolone plus strontium-89

Docetaxel and prednisolone were administered as per the control arm, for six cycles. Subject to satisfactory haematological and clinical parameters on clinical assessment 21 days after the sixth docetaxel treatment, participants received a single 150-MBq dose of Sr-89 on the 28th day after the sixth cycle.

Chemotherapy ceased after cycle 6 for Phase II participants, but for Phase III participants continued for up to 10 cycles after a period of between 28 and 56 days of Sr-89 administration, allowing for bone marrow function to be adequately recovered.

Arm D: docetaxel, prednisolone, zoledronic acid plus strontium-89

Patients in this arm received docetaxel, prednisolone and ZA for six cycles, as per arm B participants, plus clinical and haematological assessment and Sr-89 administration, as per arm C participants. Following a recovery period of between 28 and 56 days, chemotherapy, prednisolone and ZA treatment resumed until disease progression, associated treatment toxicity or patient withdrawal. As per the arm B treatment regime, following the end of chemotherapy, patients received continuing ZA administrations at 4-weekly intervals, as clinically indicated, until disease progression or until other discontinuation criteria were met. It was again recommended that patients treated with ZA also receive vitamin D and calcium supplements throughout treatment.

Further off-study treatment

All further off-study treatment, for example chemotherapy, bisphosphonate and radioisotope therapy, as well as newer drugs, such as abiraterone, enzalutamide and radium-223, received after study treatment were captured on the Concomitant Medication Running Form. The choice of further treatment was at the discretion of the participant's clinician.

Objectives

The primary objective of the Phase II component was to assess the feasibility, tolerability and safety of the four treatment arms.

Phase III assessed treatments within a two-by-two factorial design framework; that is, ZA versus no ZA (stratified for Sr-89 use) and Sr-89 versus no Sr-89 (stratified for ZA use). Each of these treatment comparisons was made in terms of clinical efficacy, with primary outcome clinical progression-free survival (CPFS) interval and health economic outcomes. In addition, the trial assessed the presence of any association between biomarkers and clinical outcomes.

Data collection

Case report forms

Data collected on each subject were recorded by the investigator or his/her designee on case report forms (CRFs). Originals of the CRF were returned to the trial management office, whereas photocopies were retained by the site.

Quality-of-life data

All eligible participants were asked to consider taking part in the QoL part of the study. QoL was assessed using patient-completed questionnaires, i.e. the European Quality of Life 5-Dimensions (EQ-5D) and Functional Assessment of Cancer Therapy – Prostate (FACT-P), while pain and analgesic use diaries were used to facilitate changes in participants' pain perception and management. An example of both the QoL booklet and pain diary are part of the protocol in *Appendix 1*. A QoL booklet and pain diary were completed at baseline and subsequently prior to each treatment and follow-up visit. Completion of these documents remained voluntary and continued throughout patient follow-up (pre and post clinical progression), irrespective of any further therapy a patient may have received.

Monitoring

The study was conducted under the auspices of the Cancer Research Clinical Trials Unit (CRCTU) according to current guidelines for good clinical practice. Participating centres were monitored by CRCTU staff to confirm compliance with the protocol and the protection of patients' rights as detailed in the Declaration of Helsinki.

Participating centres were monitored by checking incoming forms for compliance against the protocol, consistent data, missing data and timing. CRCTU onsite monitoring was carried out as detailed by the trial's risk assessment, primarily of all sites that had enrolled four or more patients into the trial. Patients' records to be audited at such visits were selected randomly from the different treatment arms.

Sample size

Sample size calculations were based on the primary outcome measure of CPFS. The calculations were the same for both the comparison of ZA with no ZA and that of Sr-89 with no Sr-89. The trial aimed to detect a HR of 0.76, which would be equivalent to 1-year CPFS rates of 30% versus 40%, assuming that CPFS follows an exponential distribution. The number of events required to detect this difference in each group for either treatment comparison, using a two-sided 5% significance level and 80% power, was 206. It was estimated that approximately 294 participants would be required in each group, that is 588 patients in total, to observe this number of events at 1 year's follow-up. We aimed to recruit a minimum of 618 evaluable patients, which allowed for 5% dropout.

The analysis of the Phase II component of the trial was entirely descriptive and did not involve any statistical hypothesis testing. The primary outcomes were feasibility, tolerability and safety, and these will be measured as proportions or means, as appropriate. Recruitment of 50 patients into each arm ensured that percentages could be estimated with a precision of at least 15% and provided sufficient data to be able to assess the arms in terms of their suitability for progression into the Phase III component of the trial.

Randomisation

Stratified randomisation

Stratification was used to ensure the balance of participant characteristics as well as numbers within each treatment group. Patients were randomised to treatment arms in a 1 : 1 : 1 : 1 allocation ratio using a computerised minimisation algorithm. If the minimisation is balanced, then allocation is random with equal chance of allocation to all arms. Randomisation was stratified by centre and ECOG performance score (0, 1 or 2) to avoid imbalance.

Implementation

Prior to randomisation, patients gave their informed consent to take part in the trial and the clinician or research nurse completed a pre-randomisation checklist to ascertain that the patient met all the entry criteria.

The process of entering a patient into the trial was conducted by telephone with the CRCTU randomisation office. Using either a computerised randomisation program or a paper equivalent should the computer system be out of commission, the CRCTU randomisation officer re-ascertained the patient's eligibility, after which the computer program allocated the next available trial number and randomised treatment arm for the participant. When the randomisation was conducted while the computer was out of commission, systems were in place to allocate the next available trial number and random treatment.

The allocated trial number and treatment arm were communicated to the site by telephone and confirmed by fax.

Follow-up

Patients were assessed every 3 weeks during the study treatment period. After treatment completion or withdrawal for any reason except disease progression (pain or tumour growth), participants were followed up monthly for 3 months and subsequently every 3 months until either patient death or withdrawal of the patient's consent for further follow-up.

Patients progressed to 3-monthly follow-up following clinical progression; that is, increasing pain, tumour growth or SREs.

Trial management

Trial Management Group

The Trial Management Group comprised the chief investigator, a few co-investigators and members of the CRCTU, as detailed in the front sleeve of the protocol (see *Appendix 1*). The Trial Management Group was responsible for the day-to-day running and management of the trial and met by teleconference or in person, as required.

Data Monitoring Committee

An independent Data Monitoring Committee (DMC; see *Appendix 2*), comprising an independent statistician, oncologist and urologist, met approximately annually to review the accumulating confidential trial data. Their main objective was to advise the Trial Steering Committee (TSC) whether or not there was any evidence or reason to amend or terminate the trial based on the recruitment rate or safety. Reports to the DMC were produced by the CRCTU.

Trial Steering Committee

An independent TSC (see *Appendix 2*) provided overall supervision for the trial and advised the trial management group. Members included an independent statistician, oncologist and two urologists. The ultimate decision regarding continuation of the trial lay with the TSC, based on the advice received from the DMC. The TSC met approximately annually, shortly after the DMC met.

Outcomes

Primary end points

Phase II: feasibility, tolerability and safety

The primary end points of the Phase II study were feasibility, tolerability and the safety of each treatment arm. Analysis was purely descriptive, while the control arm data acted as a benchmark against which to assess the experimental treatment arms. Percentages and means were calculated, and 95% confidence intervals (CIs) constructed as appropriate.

Phase III: clinical progression-free survival

The primary Phase III analysis compared ZA versus no ZA (stratified for Sr-89 use) and Sr-89 versus no Sr-89 (stratified for ZA use) in terms of CPFS. CPFS was defined as the number of whole days from the date of randomisation to the first occurrence of SRE, pain progression or death. Patients not experiencing clinical progression were censored at the date last known to be progression free.

Economic analyses

Economic evaluations were carried out to assess the cost-effectiveness of the relevant comparisons – ZA versus no ZA and Sr-89 versus no Sr-89 – for patients with mCRPC. The analyses were carried out from the perspective of the NHS and Personal Social Services and involved calculating estimates of mean per-patient costs and health outcomes for each of the compared treatment options. Costs were calculated on the

basis of treatment acquisition and administration costs, cost of concomitant medications and use of NHS primary and secondary care resources. Outcomes were expressed as quality-adjusted life-years (QALYs), calculated on the basis of patients' responses to the EQ-5D (three-level) instrument. Mean values were reported together with their 95% CIs. To account for the skewed distributions of costs and QALYs, CIs were obtained through bias-corrected and accelerated bootstrap methods. In line with current recommendations, costs and QALYs accruing in the future were discounted at an annual rate of 3.5%.

Incremental analysis was undertaken to obtain a ratio of the difference in costs over the difference in QALYs for each comparison. Results were presented in the form of incremental cost-effectiveness ratios (ICERs), reflecting the extra cost for an additional QALY.[43] To account for the inherent uncertainty as a result of sampling variation, the joint distribution of differences in cost and QALYs was derived by carrying out a large number of non-parametric bootstrap simulations.[44,45] The simulated cost and effect pairs were depicted on a cost-effectiveness plane[46] and were plotted as cost-effectiveness acceptability curves (CEACs).[47,48] A series of sensitivity analyses was carried out to assess the impact of key assumptions on the obtained results. Given the short expected survival time of mCRPC patients and the long-term follow-up of patients in the trial, lifetime costs and effects were largely observed and so extrapolation beyond the trial was not necessary.

Secondary end points

Skeletal-related event-free interval

A skeletal-related event-free interval (SREFI) was defined as the time in whole days from the date of randomisation to the date of the first occurrence of a SRE. A SRE was defined as any one of the following:

- symptomatic pathological bone fracture
- spinal cord or nerve root compression likely to be related to cancer or treatment
- cancer related surgery to bone
- radiation therapy to bone (including use of radioisotopes)
- change of antineoplastic therapy to treat bone pain due to prostate cancer
- hypercalcaemia.

Patients who did not experience a SRE were censored at death or the date last known to be alive.

Pain progression-free interval

Pain progression-free interval (PPFI) was defined as the time in whole days from the date of randomisation to the date of clinician-determined pain progression. Patients not experiencing pain progression were censored at the date of death or the date last known to be alive.

Overall survival

Overall survival was defined as the number of whole days from the date of randomisation to the date of death from any cause. Patients alive at the date of analysis were censored at the date last known to be alive.

Quality of life

Quality-of-life questionnaires included the EQ-5D, which consisted of the health-state scale, the descriptive three-level system and the visual analogue scale (VAS); the FACT-P version 4; and a health-problems questionnaire focusing predominantly on resource use. The QoL form was collected 3-weekly during treatment and then monthly for 3 months and, finally, 3-monthly until death.

The EQ-5D is a generic preference-based measure of HRQoL. The instrument was designed to be self-completed and so, where possible, data were provided by the patient. Responses to the descriptive system of the EQ-5D were translated into a single summary utility index ranging from –0.59 to 1 by using a UK-relevant value set. Patients' rating of their QoL was also collected through a vertical 20-cm VAS with the bottom end point representing the worst imaginable health state and the top end point showing the best imaginable health state. The VAS resembles a thermometer and takes values between 0 (worst imaginable state) and 100 (best imaginable state).

The FACT-P is a 40-item self-reported cancer therapy questionnaire with an additional 12-item prostate cancer subscale. Six measures were generated by this questionnaire: social well-being, personal well-being, emotional well-being, functional well-being, prostate cancer-specific score and an overall FACT-P score ranging from zero to 156.

Toxicity

The analysis of toxicity was purely descriptive. Proportions and means were calculated and 95% CIs constructed as appropriate.

Ancillary end points

Bone mineral density changes and biomarker substudies are detailed in the protocol (see *Appendix 1*); tertiary end points will not be presented at this time in this report.

Statistical methods

The definitive study analysis was conducted on an intention-to-treat basis. All tests of statistical significance were conducted at the 5% two-sided significance level. All analysis was carried out using Stata version 12.1 (StataCorp LP, College Station, TX, USA).

Descriptive comparisons not involving hypothesis testing will be presented as medians, interquartile ranges (IQRs) and ranges for numerical variables, and percentages will be given for categorical variables. Percentages will not always total exactly 100% due to rounding errors associated with reporting results to one decimal place. Percentage totals have been rounded to the nearest integer. Time-to-event analysis, multiple event analysis and QoL analysis are detailed at the start of the appropriate section. No direct statistical analysis of between randomisation arms has been conducted. The factorial design of the study assumes there is no interaction between the two agents and any treatment effects are assumed to be additive; therefore, the trial was not powered for this analysis.

Summary of changes to the trial protocol

Phase II treatment consisted of six cycles of docetaxel chemotherapy plus an additional four cycles off-study at the discretion of the treating physician. NICE, however, recommended that up to 10 cycles of docetaxel chemotherapy should be administered in one treatment block. This was not stated clearly in the Phase II protocol and the previous trial design had the inadvertent effect of preventing some patients from receiving cycles 7 to 10 at a later stage because of local policy. Adopting the NICE recommendation formally into the clinical trial design ensured that all patients had access to the NICE-recommended schedule of chemotherapy and that the control treatment arm was considered the true 'standard of care' (*Tables 3* and *4*).

TABLE 3 A summary of developmental and Phase II approved protocol versions

Protocol version no./date	Brief description of previous amendments
Versions 1–3 (12 July 2004, 2 August 2004, 16 August 2004)	• Developmental protocols not submitted for ethical or regulatory approval
TRAPEZE, Phase II: version 4 (1 September 2004)	• First approved and implemented version
Version 5 (23 March 2005)	• Change to the eligibility criteria to enable patients to enter the study without the need for a confirmation prostate biopsy if they have confirmed bone disease with a PSA value of $\geq$ 100 ng/ml • Change to wording of baseline and post-chemotherapy assessment requirements to allow centres to take part in the study without the need to perform clinical procedures if local facilities are not available
Version 6 (7 June 2005)	• Safety amendment to clarification of ZA dose procedures to comply with the manufacturer's summary of product characteristics
Version 7 (4 May 2007)	• Changes to the inclusion criteria clarified patient eligibility regarding abnormal ALT and AST levels • The requirement for a confirmed serum testosterone blood test was removed from the screening procedures • A new entry criterion question was added to ensure that at time of study entry all patients were fit enough to receive any of the trial treatments, in the opinion of the investigator • Clarification of administration sequence of trial treatments

ALT, alanine aminotransferase; AST, aspartate aminotransferase.

TABLE 4 A summary of Phase III approved protocol versions

TRAPEZE, Phase III: version 8 (24 September 2008)	• The majority of the changes related to the transition from a Phase II to a Phase III clinical trial, covering trial infrastructure, data collection procedures and statistical considerations. These changes had no direct impact on patient participation or safety but did increase the maximum number of chemotherapy cycles from 6 to 10, according to NICE guidelines for docetaxel chemotherapy
Version 9 (12 April 2011)	• This amendment concerns a statistical redesign of the Phase III trial from a four-arm comparison to a two-by-two factorial design to assess treatment efficacy • Reduction of target recruitment from 1240 (as per version 8 amendment) to 618 evaluable patients. The trial will close to recruitment at the end of February 2012
Version 10 (25 May 2011)	• This amendment concerns a correction in section 12.2.3 on timing of analysis. We intend to conduct initial analysis once all patients have at least 1 year's follow-up, not 2 years as previously stated
Version 11 (17 February 2012)	Substantial amendments: • Changing the requirement for both ALT and AST to be tested – only one of them needs to have been performed • Change of definition for SRE-free interval and PPFI, and removal of the event of death as a SRE and element of pain progression criteria Non-substantial amendments: • Clarification of prophylactic antiemetic for nausea/vomiting because of chemotherapy and permission to use local protocols that coincide with off-study practice • Updating of deputy clinical co-ordinator's details • Additional safety information for ZA administration Various typographical corrections and clarifications of existing text

ALT, alanine aminotransferase; AST, aspartate aminotransferase.

Chapter 3 Results

Consolidated Standards of Reporting Trials diagram

A Consolidated Standards of Reporting Trials (CONSORT) diagram summarising trial participation figures and analysis is included as *Figure 6*.

Recruitment

Figure 7 shows trial recruitment both by monthly randomisation periods and cumulatively over the course of the trial. *Table 78* (see *Appendix 5*) shows recruitment by centre.

Losses and exclusions

Ineligible

In total, 27 patients were found to be ineligible following randomisation. Five were randomised to docetaxel alone, 10 to docetaxel + ZA, seven to docetaxel + Sr-89 and five to docetaxel, ZA and Sr-89. All ineligible patients are included in intention-to-treat analysis.

There were three main categories of ineligibilities. These were (1) pre-randomisation blood pressure and blood tests were missed or performed outside of the allowed time frame, (2) progression on trial entry was not appropriately documented and (3) hormone therapies were not stopped at the appropriate time point, for example if bicalutamide had been stopped within 4 weeks of starting trial treatment rather than within 4 weeks of randomisation as stipulated in the eligibility criteria.

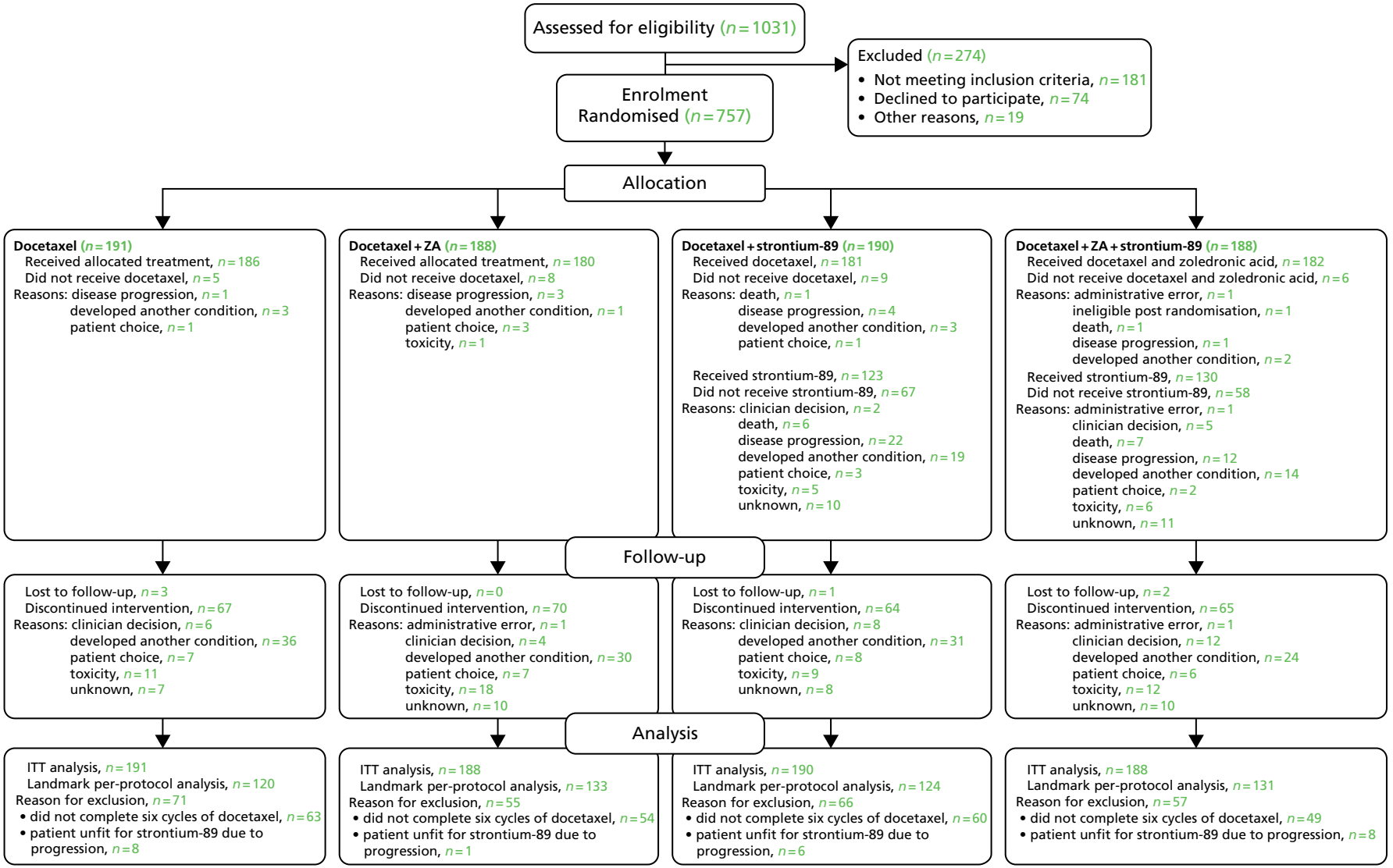


FIGURE 6 Consolidated Standards of Reporting Trials (CONSORT) diagram. ITT, intention to treat.

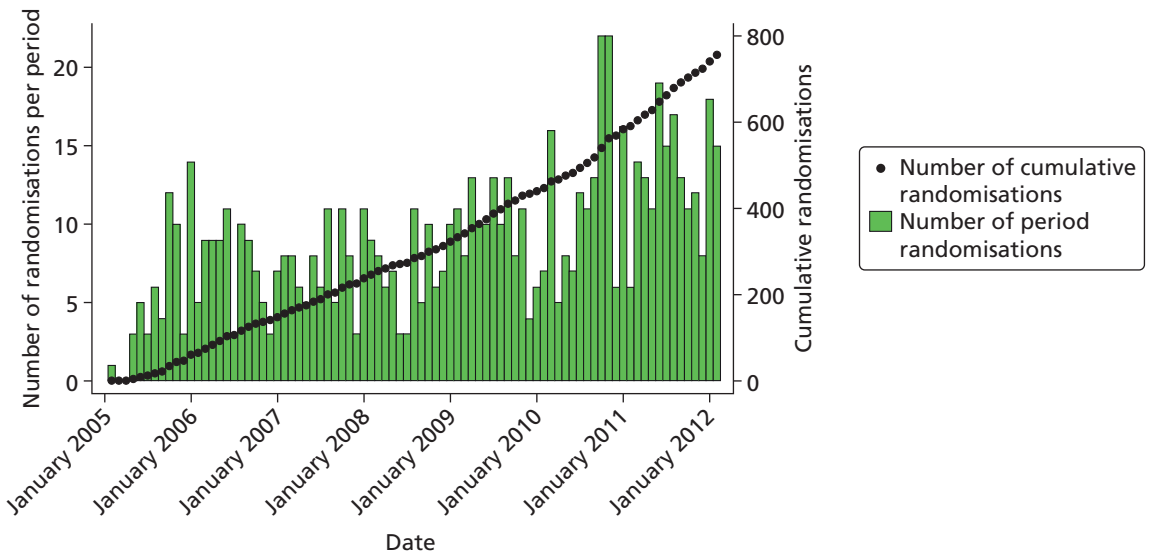


FIGURE 7 Recruitment from January 2005 to February 2012.

Protocol deviations

In total, 71 protocol deviations were reported: 15 in the docetaxel arm, 17 in the docetaxel and ZA arm, 18 in the docetaxel and Sr-89 arm and 21in the docetaxel, ZA and Sr-89 arm.

Table 5 provides a complete summary of all protocol deviations reported during the course of the trial.

Patient withdrawal of consent

Full consent for any further participation in the trial, including follow-up, has been withdrawn by 21 patients. In addition, 28 patients have withdrawn from one or more of the trial substudies. *Table 6* contains a breakdown of all non-treatment withdrawals by randomisation arm and *Table 7* by comparison group; a complete list of all patients who have withdrawn full consent can be found in *Appendix 5*.

Withdrawal of trial treatment

Docetaxel

In total, 408 (54%) patients received fewer than the protocol-defined number of treatment cycles, which was originally six and then increased to 10. In total, 220 (29%) patients received only six cycles because of the original protocol limitation. *Table 8* shows the reasons for withdrawal from docetaxel by randomisation arm and *Table 9* shows the reasons by comparison group.

Strontium-89

Of the 378 patients randomised to receive Sr-89, 253 (67%) did so. The reasons for not receiving Sr-89 are reported in *Table 10*.

Lost to follow-up

Six patients in total have been reported as being lost to follow-up by site: three randomised to docetaxel alone, one randomised to docetaxel and Sr-89 and two randomised to docetaxel, ZA and Sr-89. Two of these reached the primary end point prior to being lost, one subsequently died and, although some follow-up information remains missing, the death information was obtained.

TABLE 5 Reasons for deviations

Deviation reason	*n* (*N* = 71)
Administrative error	2
Blood pressure consistently not done	2
Blood pressure not done at baseline	10
Bloods not done before chemotherapy	1
Calcium supplements not given with ZA	1
Calcium supplements stopped at incorrect time for Sr-89	1
Chemotherapy capped at wrong BSA	9
Clinician chose to give lower dose of docetaxel because of patient's age and comorbidities	1
Cycle delayed over 14 days	6
Docetaxel dose capped at BSA of 2 m^2 by medical decision to prevent possible excess toxicity	1
Docetaxel dose escalated	1
Docetaxel dose reduction not per protocol	7
Dose not recalculated to BSA at cycle 5: 160 mg given instead of 150 mg	1
Incorrect dose of strontium	1
Patient did not receive scheduled ZA	1
Patient received intended dose of 67.2 mg/m^2 because of diarrhoea	1
Patient received different trial arm	5
Patient recommenced bicalutamide while on study	1
Patient sensitive to prednisolone, therefore commenced on 1.5 mg of dexamethasone	1
Patient stopped taking LHRH agonist	1
Post-docetaxel assessment not done prior to Sr-89	6
Post-docetaxel assessment performed late	1
Pre-ZA creatinine not done	2
Premature discontinuation	2
Sr-89 given at wrong time point	5
Sr-89 given prior to post-docetaxel assessment	1
Total	71

BSA, body surface area; LHRH, luteinising hormone-releasing hormone.

TABLE 6 Withdrawal: by randomisation arm

	Docetaxel (*N* = 191)		Docetaxel + ZA (*N* = 188)		Docetaxel + Sr-89 (*N* = 190)		Docetaxel + ZA + Sr-89 (*N* = 188)		Overall (*N* = 757)	
Withdrawal	***n***	**%**	***n***	**%**	***n***	**%**	***n***	**%**	***n***	**%**
Full withdrawal of consent	6	3.1	13	6.9	6	3.2	3	1.6	28	3.7
No withdrawal	178	93.2	168	89.4	177	93.2	174	92.6	697	92.1
Partial withdrawal: blocks	0	0.0	0	0.0	0	0.0	1	0.5	1	0.1
Partial withdrawal: proteomics	0	0.0	1	0.5	0	0.0	1	0.5	2	0.3
Partial withdrawal: QoI	7	3.7	5	2.7	7	3.7	5	2.7	24	3.2
Partial withdrawal: QoI + blocks	0	0.0	1	0.5	0	0.0	0	0.0	1	0.1
Partial withdrawal: QoI + proteomics	0	0.0	0	0.0	0	0.0	4	2.1	4	0.5
Total	191	100	188	100	190	100	188	100	757	100

TABLE 7 Withdrawal: by comparison group

	No ZA (*N* = 381)		ZA (*N* = 376)		No Sr-89 (*N* = 379)		Sr-89 (*N* = 378)	
Withdrawal	***n***	**%**	***n***	**%**	***n***	**%**	***n***	**%**
Full withdrawal of consent	12	3.1	16	4.3	19	5	9	2.4
No withdrawal	355	93.2	342	91	346	91.3	351	92.9
Partial withdrawal: blocks	0	0.0	1	0.3	0	0.0	1	0.3
Partial withdrawal: proteomics	0	0.0	2	0.5	1	0.3	1	0.3
Partial withdrawal: QoI	14	3.7	10	2.7	12	3.2	12	3.2
Partial withdrawal: QoI + blocks	0	0.0	1	0.3	1	0.3	0	0.0
Partial withdrawal: QoI + proteomics	0	0.0	4	1.1	0	0.0	4	1.1
Total	381	100	376	100	379	100	378	100

TABLE 8 Docetaxel withdrawal by randomisation arms

	Docetaxel (*N* = 107)		Docetaxel + ZA (*N* = 100)		Docetaxel + Sr-89 (*N* = 106)		Docetaxel + ZA + Sr-89 (*N* = 95)		Overall (*N* = 408)	
Withdrawal reason	***n***	**%**	***n***	**%**	***n***	**%**	***n***	**%**	***n***	**%**
Administration error	0	0.0	1	1.0	0	0.0	1	1.1	2	0.5
Change in treatment	4	3.7	1	1.0	3	2.8	4	4.2	12	2.9
Clinician decision	2	1.9	3	3.0	5	4.7	8	8.4	18	4.4
Death	5	4.7	3	3.0	9	8.5	7	7.4	24	5.9
Disease progression	35	32.7	27	27.0	33	31.1	23	24.2	118	28.9
Other condition	36	33.6	30	30.0	31	29.2	24	25.3	121	29.7
Patient choice	7	6.5	7	7.0	8	7.5	6	6.3	28	6.9
Toxicity	11	10.3	18	18.0	9	8.5	12	12.6	50	12.3
Unknown	7	6.5	10	10.0	8	7.5	10	10.5	35	8.6
Total	107	100.0	100	100.0	106	100.0	95	100.0	408	100.0

TABLE 9 Docetaxel withdrawal by comparison groups

	No ZA		ZA		No Sr-89		Sr-89	
Withdrawal reason	***n***	**%**	***n***	**%**	***n***	**%**	***n***	**%**
Administration error	0	0.0	2	1.0	1	0.5	1	0.5
Change in treatment	7	3.3	5	2.6	5	2.4	7	3.5
Clinician decision	7	3.3	11	5.6	5	2.4	13	6.5
Death	14	6.6	10	5.1	8	3.9	16	8.0
Disease progression	68	32.0	50	25.6	62	29.9	56	27.9
Other condition	67	31.4	54	27.7	66	31.9	55	27.4
Patient choice	15	7.0	13	6.7	14	6.8	14	6.9
Toxicity	20	9.4	30	15.4	29	14.0	21	10.4
Unknown	15	7.0	20	10.3	17	8.2	18	8.9
Total	213	100.0	195	100.0	207	100.0	201	100.0

TABLE 10 Reasons for Sr-89 omission

	Docetaxel + Sr-89 (*N* = 67)		Docetaxel + ZA + Sr-89 (*N* = 58)		Overall (*N* = 125)	
Withdrawal reason	***n***	**%**	***n***	**%**	***n***	**%**
Administration error	0	0.0	1	1.7	1	0.8
Change in treatment	2	3.0	3	5.2	5	4.0
Clinician decision	0	0.0	2	3.4	2	1.6
Death	6	9.0	7	12.1	13	10.4
Disease progression	22	32.8	12	20.7	34	27.2
Other condition	19	28.4	14	24.1	33	26.4
Patient choice	3	4.5	2	3.4	5	4.0
Toxicity	5	7.5	6	10.3	11	8.8
Unknown	10	14.9	11	19.0	21	16.8
Total	67	100.0	58	100.0	125	100.0

Data maturity

In total, 618 patients have been followed up until death. Of the remaining 139 patients, 78 have reached the primary CPFS end point, leaving 61 patients alive without having reached the primary end point.

The average follow-up of alive patients was 1.84 years (IQR 1.4–2.4 years), and the average follow-up of the 61 patients who have not reached the primary end point was 1.7 years (IQR 1.4–2.1 years). *Table 11* shows the average follow-up of the surviving patients split by randomisation arm.

Figure 8 shows the time between the date of randomisation and the date when the patient was last seen and the time from that date to the date of the analysis. Each point represents a patient, and the solid black dots are patients who have not reached the primary end point of the trial. The solid black line indicates where the patients would appear on the graph if they were seen on the date of the analysis. The dashed line represents 6 months before the analysis and the dotted line represents 12 months prior to the analysis.

TABLE 11 Follow-up of alive patients

Duration of follow-up (years)	Docetaxel (*N* = 37)	Docetaxel + ZA (*N* = 32)	Docetaxel + Sr-89 (*N* = 35)	Docetaxel + ZA + Sr-89 (*N* = 35)	Overall (*N* = 139)
n	37	32	35	35	139
Median	1.7	1.8	1.9	1.9	1.8
IQR	1.4–2.3	1.4–2.3	1.6–2.6	1.5–2.4	1.4–2.4

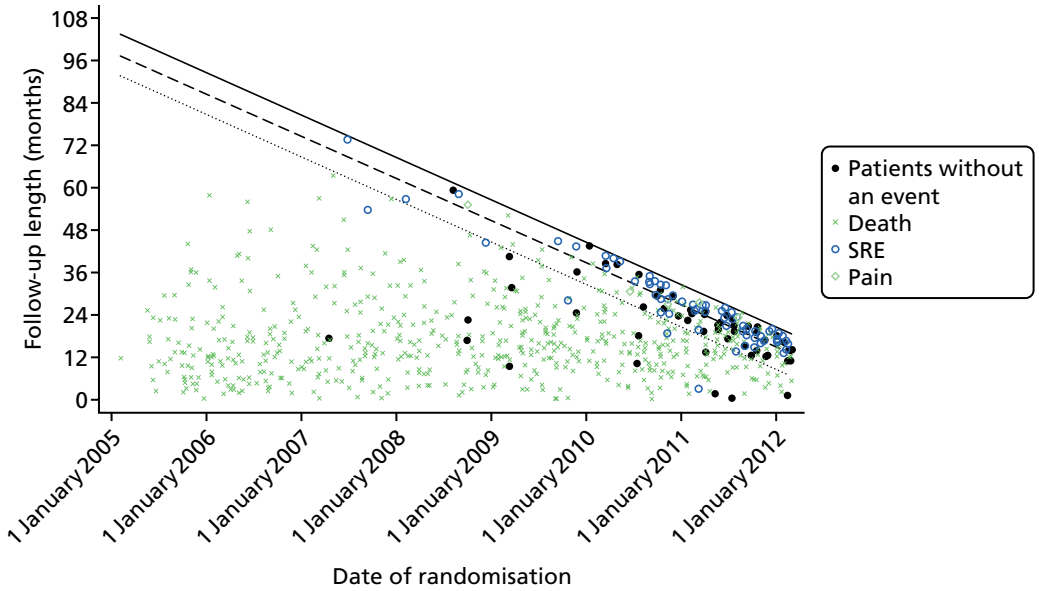


FIGURE 8 Duration of follow-up. Pain, pain progression.

Stratification variables

Two stratification factors were used during the randomisation process: centre and ECOG performance status. These can be seen in *Tables 12* and *13*.

TABLE 12 Stratification variables by randomisation arm

	Docetaxel (*N* = 191)		Docetaxel + ZA (*N* = 188)		Docetaxel + Sr-89 (*N* = 190)		Docetaxel + ZA + Sr-89 (*N* = 188)		Overall (*N* = 757)	
Stratification variable	***n***	**%**	***n***	**%**	***n***	**%**	***n***	**%**	***n***	**%**
ECOG performance status score										
0	77	40.3	76	40.4	76	40.0	76	40.4	305	40.3
1	98	51.3	97	51.6	97	51.1	97	51.6	389	51.4
2	16	8.4	15	8.0	17	8.9	15	8.0	63	8.3
Randomisation centre										
Aberdeen Royal Infirmary	5	2.6	5	2.7	5	2.6	6	3.2	21	2.8
Ayr Hospital	5	2.6	6	3.2	5	2.6	5	2.7	21	2.8
Beatson West of Scotland Cancer Centre	15	7.9	15	8.0	15	7.9	16	8.5	61	8.1
Bradford Royal Infirmary	3	1.6	4	2.1	4	2.1	2	1.1	13	1.7
Cheltenham General Hospital	4	2.1	4	2.1	4	2.1	4	2.1	16	2.1
Christie Hospital	30	15.7	31	16.5	30	15.8	31	16.5	122	16.1
Dorset County Hospital	2	1.0	1	0.5	1	0.5	1	0.5	5	0.7
Forth Valley Royal Hospital	2	1.0	1	0.5	2	1.1	1	0.5	6	0.8
Gloucester Royal Hospital	0	0.0	0	0.0	1	0.5	0	0.0	1	0.1
Huddersfield Royal Infirmary	2	1.0	2	1.1	3	1.6	2	1.1	9	1.2
Ipswich Hospital	5	2.6	4	2.1	4	2.1	4	2.1	17	2.2
Maidstone Hospital	7	3.7	7	3.7	7	3.7	8	4.3	29	3.8
Poole Hospital	0	0.0	5	0.0	0	0.0	1	0.5	1	0.1
Queen Alexandra Hospital	4	2.1	6	2.7	4	2.1	4	2.1	17	2.2
Queen Elizabeth Hospital	32	16.8	15	16.5	32	16.8	31	16.5	126	16.6
Royal Albert Edward Infirmary	2	1.0	4	0.5	2	1.1	2	1.1	7	0.9
Royal Bournemouth Hospital	2	1.0	4	0.5	1	0.5	1	0.5	5	0.7
Royal Derby Hospital	6	3.1	31	3.2	7	3.7	7	3.7	26	3.4
Royal Free Hospital	3	1.6	1	2.1	2	1.1	3	1.6	12	1.6
Royal Marsden Hospital London	1	0.5	1	0.0	0	0.0	0	0.0	1	0.1
Royal Marsden Hospital Sutton	7	3.7	0	4.3	7	3.7	8	4.3	30	4.0
Royal Preston Hospital	9	4.7	2	4.8	8	4.2	8	4.3	34	4.5
Southampton General Hospital	4	2.1	4	1.6	4	2.1	3	1.6	14	1.8
St James's University Hospital	7	3.7	7	3.7	7	3.7	6	3.2	27	3.6
Velindre Hospital	1	0.5	5	1.1	2	1.1	2	1.1	7	0.9
Western General Hospital	28	14.7	6	14.4	28	14.7	28	14.9	111	14.7
Weston General Hospital	3	1.6	15	1.6	4	2.1	3	1.6	13	1.7
Wishaw General Hospital	2	1.0	4	0.5	1	0.5	1	0.5	5	0.7

TABLE 13 Stratification variables by comparison group

	No ZA (*N* = 381)		ZA (*N* = 376)		No Sr-89 (*N* = 379)		Sr-89 (*N* = 378)	
Stratification variable	***n***	**%**	***n***	**%**	***n***	**%**	***n***	**%**
ECOG performance status score								
0	153	40.2	152	40.4	153	40.4	152	40.2
1	195	51.2	194	51.6	195	51.5	194	51.3
2	33	8.7	30	8.0	31	8.2	32	8.5
Randomisation centre								
Aberdeen Royal Infirmary	10	2.6	11	2.9	10	2.6	11	2.9
Ayr Hospital	10	2.6	11	2.9	11	2.9	10	2.6
Beatson West of Scotland Cancer Centre	30	7.9	31	8.2	30	7.9	31	8.2
Bradford Royal Infirmary	7	1.8	6	1.6	7	1.8	6	1.6
Cheltenham General Hospital	8	2.1	8	2.1	8	2.1	8	2.1
Christie Hospital	60	15.7	62	16.5	61	16.1	61	16.1
Dorset County Hospital	3	0.8	2	0.5	3	0.8	2	0.5
Forth Valley Royal Hospital	4	1.0	2	0.5	3	0.8	3	0.8
Gloucester Royal Hospital	1	0.3	0	0.0	0	0.0	1	0.3
Huddersfield Royal Infirmary	5	1.3	4	1.1	4	1.1	5	1.3
Ipswich Hospital	9	2.4	8	2.1	9	2.4	8	2.1
Maidstone Hospital	14	3.7	15	4.0	14	3.7	15	4.0
Poole Hospital	0	0.0	1	0.3	0	0.0	1	0.3
Queen Alexandra Hospital	8	2.1	9	2.4	9	2.4	8	2.1
Queen Elizabeth Hospital	64	16.8	62	16.5	63	16.6	63	16.7
Royal Albert Edward Infirmary	4	1.0	3	0.8	3	0.8	4	1.1
Royal Bournemouth Hospital	3	0.8	2	0.5	3	0.8	2	0.5
Royal Derby Hospital	13	3.4	13	3.5	12	3.2	14	3.7
Royal Free Hospital	5	1.3	7	1.9	7	1.8	5	1.3
Royal Marsden Hospital London	1	0.3	0	0.0	1	0.3	0	0.0
Royal Marsden Hospital Sutton	14	3.7	16	4.3	15	4.0	15	4.0
Royal Preston Hospital	17	4.5	17	4.5	18	4.7	16	4.2
Southampton General Hospital	8	2.1	6	1.6	7	1.8	7	1.9
St James's University Hospital	14	3.7	13	3.5	14	3.7	13	3.4
Velindre Hospital	3	0.8	4	1.1	3	0.8	4	1.1
Western General Hospital	56	14.7	55	14.6	55	14.5	56	14.8
Weston General Hospital	7	1.8	6	1.6	6	1.6	7	1.9
Wishaw General Hospital	3	0.8	2	0.5	3	0.8	2	0.5

Baseline data

In total, 752 (99%) baseline forms were returned. *Table 14* shows the baseline information recorded on the on-study form by randomisation arm.

Table 15 repeats the baseline characteristics reported above but split by comparison groups.

TABLE 14 Patient characteristics by randomisation arm

	Randomisation arm									
	Docetaxel (*N* = 191)		Docetaxel + ZA (*N* = 187)		Docetaxel + Sr-89 (*N* = 188)		Docetaxel + ZA + Sr-89 (*N* = 186)		Overall (*N* = 752)	
Patient characteristic	*n*	%	*n*	%	*n*	%	*n*	%	*n*	%
ECOG performance status score										
0	76	43.4	71	40.8	70	39.3	64	37.0	281	40.1
1	83	47.4	88	50.6	90	50.6	95	54.9	356	50.9
2	15	8.6	15	8.6	18	10.1	14	8.1	62	8.9
3	1	0.6	0	0.0	0	0.0	0	0.0	1	0.1
Missing	16	–	13	–	10	–	13	–	52	–
Diagnostic indicator										
Adenocarcinoma	156	81.7	146	78.9	150	80.2	149	81.0	601	80.5
PSA only	35	18.3	39	21.1	37	19.8	35	19.0	146	19.5
Missing	0	–	2	–	1	–	2	–	5	–
Staging: T										
T1	2	1.4	5	3.8	2	1.7	1	0.7	10	1.9
T1b	1	0.7	0	0.0	1	0.8	0	0.0	2	0.4
T1c	0	0.0	1	0.8	2	1.7	1	0.7	4	0.7
T2	19	13.3	16	12.2	11	9.1	17	12.1	63	11.8
T2a	2	1.4	2	1.5	0	0.0	0	0.0	4	0.7
T2b	4	2.8	1	0.8	1	0.8	2	1.4	8	1.5
T3	54	37.8	53	40.5	49	40.5	63	44.7	219	40.9
T3a	4	2.8	3	2.3	5	4.1	4	2.8	16	3.0
T3b	12	8.4	10	7.6	10	8.3	9	6.4	41	7.6
T4	28	19.6	22	16.8	20	16.5	25	17.7	95	17.7
TX	16	11.2	18	13.7	20	16.5	18	12.8	72	13.4
T2c	1	0.7	0	0.0	0	0.0	1	0.7	2	0.4
Missing	48	–	56	–	67	–	45	–	216	–

TABLE 14 Patient characteristics by randomisation arm (*continued*)

	Randomisation arm									
	Docetaxel (*N* = 191)		Docetaxel + ZA (*N* = 187)		Docetaxel + Sr-89 (*N* = 188)		Docetaxel + ZA + Sr-89 (*N* = 186)		Overall (*N* = 752)	
Patient characteristic	*n*	%	*n*	%	*n*	%	*n*	%	*n*	%
Staging: M										
M0	44	30.8	41	31.3	33	27.3	40	28.4	158	29.5
M1a	20	14.0	20	15.3	22	18.2	21	14.9	83	15.5
M1b	8	5.6	7	5.3	3	2.5	2	1.4	20	3.7
M1c	4	2.8	10	7.6	6	5.0	5	3.5	25	4.7
MX	26	18.2	14	10.7	17	14.0	26	18.4	83	15.5
M1	41	28.7	39	29.8	40	33.1	47	33.3	167	31.2
Missing	48	–	56	–	67	–	45	–	216	–
Staging: N										
N0	59	41.3	57	43.5	46	38.0	58	41.1	220	41.0
N1	42	29.4	28	21.4	32	26.4	39	27.7	141	26.3
NX	42	29.4	46	35.1	43	35.5	44	31.2	175	32.6
Missing	48	–	56	–	67	–	45	–	216	–
Gleason score										
3	0	0.0	0	0.0	0	0.0	1	0.7	1	0.2
4	2	1.4	0	0.0	1	0.7	0	0.0	3	0.5
5	2	1.4	3	2.1	2	1.4	3	2.2	10	1.8
6	9	6.3	12	8.4	12	8.7	6	4.5	39	7.0
7	43	29.9	48	33.6	39	28.3	41	30.6	171	30.6
8	30	20.8	24	16.8	35	25.4	25	18.7	114	20.4
9	57	39.6	55	38.5	41	29.7	54	40.3	207	37.0
10	1	0.7	1	0.7	8	5.8	4	3.0	14	2.5
Missing	47	–	44	–	50	–	52	–	193	–
Prior radiotherapy received?										
No	114	59.7	107	57.2	95	50.8	98	52.7	414	55.1
Yes	77	40.3	80	42.8	92	49.2	88	47.3	337	44.9
Missing	0	–	0	–	1	–	0	–	1	–
Method of castration										
Surgery	5	2.6	4	2.1	3	1.6	2	1.1	14	1.9
Ongoing LHRH agonists	186	97.4	183	97.9	185	98.4	184	98.9	738	98.1
Anti-androgen received?										
No	10	5.2	19	10.2	17	9.1	14	7.6	60	8.0
Yes	181	94.8	168	89.8	170	90.9	171	92.4	690	92.0
Missing	0	–	0	–	1	–	1	–	2	–

continued

TABLE 14 Patient characteristics by randomisation arm (*continued*)

	Randomisation arm									
	Docetaxel (*N* = 191)		Docetaxel + ZA (*N* = 187)		Docetaxel + Sr-89 (*N* = 188)		Docetaxel + ZA + Sr-89 (*N* = 186)		Overall (*N* = 752)	
Patient characteristic	*n*	%	*n*	%	*n*	%	*n*	%	*n*	%
Flutamide, nilutamide or cyproterone acetate received?										
No	151	83.9	141	83.9	142	84.0	133	77.8	567	82.4
Yes	29	16.1	27	16.1	27	16.0	38	22.2	121	17.6
Missing	11	–	19	–	19	–	15	–	64	–
Bicalutamide received?										
No	11	6.1	14	8.3	8	4.7	15	8.8	48	7.0
Yes	170	93.9	154	91.7	162	95.3	156	91.2	642	93.0
Missing	10	–	19	–	18	–	15	–	62	–
Method of progression at study entry										
All	26	13.7	27	14.6	27	14.4	27	14.5	107	14.3
Elevated PSA	42	22.1	48	25.9	42	22.3	44	23.7	176	23.5
New lesion	15	7.9	16	8.6	21	11.2	19	10.2	71	9.5
Objective	5	2.6	1	0.5	1	0.5	1	0.5	8	1.1
Objective + new lesion	3	1.6	4	2.2	7	3.7	5	2.7	19	2.5
PSA + new lesion	94	49.5	85	45.9	82	43.6	88	47.3	349	46.6
PSA + objective	5	2.6	4	2.2	8	4.3	2	1.1	19	2.5
Missing	1	–	2	–	0	–	0	–	3	–
Baseline pain diary completed?										
No	30	15.7	37	19.8	42	22.3	34	18.3	143	19.0
Yes	161	84.3	150	80.2	146	77.7	152	81.7	609	81.0
Baseline QoL booklet completed?										
No	22	11.6	19	10.3	28	14.9	25	13.7	94	12.6
Yes	168	88.4	165	89.7	160	85.1	158	86.3	651	87.4
Missing	1	–	3	–	0	–	3	–	7	–

LHRH, luteinising hormone-releasing hormone.

TABLE 15 Patient characteristics by comparison group

	Comparison group							
	No ZA (*N* = 379)		ZA (*N* = 373)		No Sr-89 (*N* = 378)		Sr-89 (*N* = 374)	
Patient characteristic	*n*	%	*n*	%	*n*	%	*n*	%
ECOG performance status score								
0	146	41.4	135	38.9	147	42.1	134	38.2
1	173	49.0	183	52.7	171	49.0	185	52.7
2	33	9.3	29	8.4	30	8.6	32	9.1
3	1	0.3	0	0.0	1	0.3	0	0.0
Missing	26	–	26	–	29	–	23	–
Diagnostic indicator								
Adenocarcinoma	306	81.0	295	79.9	302	80.3	299	80.6
PSA only	72	19.0	74	20.1	74	19.7	72	19.4
Missing	1	–	4	–	2	–	3	–
Staging: T								
T1	4	1.5	6	2.2	7	2.6	3	1.1
T1b	2	0.8	0	0.0	1	0.4	1	0.4
T1c	2	0.8	2	0.7	1	0.4	3	1.1
T2	30	11.4	33	12.1	35	12.8	28	10.7
T2a	2	0.8	2	0.7	4	1.5	0	0.0
T2b	5	1.9	3	1.1	5	1.8	3	1.1
T3	103	39.0	116	42.6	107	39.1	112	42.7
T3a	9	3.4	7	2.6	7	2.6	9	3.4
T3b	22	8.3	19	7	22	8.0	19	7.3
T4	48	18.2	47	17.3	50	18.2	45	17.2
TX	36	13.6	36	13.2	34	12.4	38	14.5
T2c	1	0.4	1	0.4	1	0.4	1	0.4
Missing	115	–	101	–	104	–	112	–
Staging: M								
M0	77	29.2	81	29.8	85	31.0	73	27.9
M1a	42	15.9	41	15.1	40	14.6	43	16.4
M1b	11	4.2	9	3.3	15	5.5	5	1.9
M1c	10	3.8	15	5.5	14	5.1	11	4.2
MX	43	16.3	40	14.7	40	14.6	43	16.4
M1	81	30.7	86	31.6	80	29.2	87	33.2
Missing	115	–	101	–	104	–	112	–
Staging: N								
N0	105	39.8	115	42.3	116	42.3	104	39.7
N1	74	28.0	67	24.6	70	25.5	71	27.1
NX	85	32.2	90	33.1	88	32.1	87	33.2
Missing	115	–	101	–	104	–	112	–

continued

TABLE 15 Patient characteristics by comparison group (*continued*)

Patient characteristic	Comparison group							
	No ZA (*N* = 379)		ZA (*N* = 373)		No Sr-89 (*N* = 378)		Sr-89 (*N* = 374)	
	n	%	*n*	%	*n*	%	*n*	%
Gleason score								
3	0	0.0	1	0.4	0	0.0	1	0.4
4	3	1.1	0	0.0	2	0.7	1	0.4
5	4	1.4	6	2.2	5	1.7	5	1.8
6	21	7.4	18	6.5	21	7.3	18	6.6
7	82	29.1	89	32.1	91	31.7	80	29.4
8	65	23.0	49	17.7	54	18.8	60	22.1
9	98	34.8	109	39.4	112	39.0	95	34.9
10	9	3.2	5	1.8	2	0.7	12	4.4
Missing	97	–	96	–	91	–	102	–
Prior radiotherapy received?								
No	209	55.3	205	55.0	221	58.5	193	51.7
Yes	169	44.7	168	45.0	157	41.5	180	48.3
Missing	1	–	–	–	–	–	1	–
Method of castration								
Surgery	8	2.1	6	1.6	9	2.4	5	1.3
Ongoing LHRH agonists	371	97.9	367	98.4	369	97.6	369	98.7
Anti-androgen received?								
No	27	7.1	33	8.9	29	7.7	31	8.3
Yes	351	92.9	339	91.1	349	92.3	341	91.7
Flutamide, nilutamide or cyproterone acetate received?								
No	293	84.0	274	80.8	292	83.9	275	80.9
Yes	56	16.0	65	19.2	56	16.1	65	19.1
Missing	30	–	34	–	30	–	34	–
Bicalutamide received?								
No	19	5.4	29	8.6	25	7.2	23	6.7
Yes	332	94.6	310	91.4	324	92.8	318	93.3
Missing	28	–	34	–	29	–	33	–
Method of progression at study entry								
All	53	14.0	54	14.6	53	14.1	54	14.4
Elevated PSA	84	22.2	92	24.8	90	24.0	86	23.0
New lesion	36	9.5	35	9.4	31	8.3	40	10.7
Objective	6	1.6	2	0.5	6	1.6	2	0.5
Objective + new lesion	10	2.6	9	2.4	7	1.9	12	3.2
PSA + new lesion	176	46.6	173	46.6	179	47.7	170	45.5
PSA + objective	13	3.4	6	1.6	9	2.4	10	2.7
Missing	1	–	2	–	3	–	0	–

TABLE 15 Patient characteristics by comparison group (*continued*)

	Comparison group							
	No ZA (*N* = 379)		ZA (*N* = 373)		No Sr-89 (*N* = 378)		Sr-89 (*N* = 374)	
Patient characteristic	*n*	%	*n*	%	*n*	%	*n*	%
Baseline pain diary completed?								
No	72	19.0	71	19.0	67	17.7	76	20.3
Yes	307	81.0	302	81.0	311	82.3	298	79.7
Baseline QoL booklet completed?								
No	50	13.2	44	12.0	41	11.0	53	14.3
Yes	328	86.8	323	88.0	333	89.0	318	85.7
Missing	1	–	6	–	4	–	3	–
	n		*n*		*n*		*n*	
Age at randomisation (years)								
N	379		373		378		374	
Median	68.4		69.0		68.9		68.6	
IQR	63.6–73.6		64.1–73.4		64.3–73.8		63.2–73.1	
Range	45.9–83.8		45.0–83.7		45.0–83.8		49.4–82.0	
Days from baseline ECOG to randomisation								
N	349		339		341		347	
Median	2.0		2.0		2.0		2.0	
IQR	0.0–8.0		0.0–8.0		0.0–8.0		0.0–7.0	
Range	0.0–367.0		0.0–73.0		0.0–51.0		0.0–367.0	
Months from diagnosis to randomisation								
N	379		373		378		374	
Median	30.1		37.8		34.0		33.3	
IQR	18.7–61.6		20.2–62.1		19.2–57.0		19.0–70.1	
Range	1.3–246.2		0.3–190.3		0.3–246.2		0.4–187.2	

LHRH, luteinising hormone-releasing hormone.

Treatment

In total, 4488 treatment forms were returned. *Table 16* shows the treatment information split by cycle for each of the randomisation arms and *Table 17* shows the same details split by comparison groups. The data show that only 17% of patients received 10 cycles of docetaxel, with 45% stopping at cycle 6. It is important to take into account that 29% of patients were only ever intended to receive six cycles of treatment, as previously detailed in *Withdrawal of trial treatment*, *docetaxel*.

The 47 reasons for discontinuation of ZA which are reported as 'other' in *Table 16* are summarised in *Table 18*.

TABLE 16 Treatment details by randomisation arm

Treatment details	Cycle									
	C1 (*N* = 729)	C2 (*N* = 692)	C3 (*N* = 665)	C4 (*N* = 623)	C5 (*N* = 588)	C6 (*N* = 527)	C7 (*N* = 202)	C8 (*N* = 179)	C9 (*N* = 154)	C10 (*N* = 129)
Docetaxel: days since randomisation										
n	186	179	170	158	148	128	45	38	34	26
Median	6.0	28.0	49.0	70.0	91.0	112.0	133.0	154.0	175.5	196.0
IQR	2.0–8.0	24.0–31.0	45.0–54.0	67.0–76.0	88.0–98.0	110.0–119.0	130.0–140.0	151.0–162.0	173.0–183.0	194.0–204.0
Docetaxel + ZA: days since randomisation										
n	180	167	163	156	148	132	57	53	43	34
Median	6.0	27.0	49.0	70.0	91.0	113.0	135.0	156.0	178.0	199.0
IQR	3.0–9.0	24.0–32.0	45.0–53.0	67.5–75.0	88.0–97.0	110.0–119.0	131.0–139.0	152.0–161.0	173.0–183.0	194.0–203.0
Docetaxel + Sr-89: days since randomisation										
n	181	175	166	152	144	130	49	44	40	35
Median	7.0	28.0	49.0	70.0	92.0	113.0	174.0	195.5	218.0	241.0
IQR	3.0–9.0	25.0–31.0	46.0–53.0	68.0–74.0	89.0–97.0	110.0–118.0	170.0–183.0	190.5–205.0	212.5–228.0	233.0–254.0
Docetaxel + ZA + Sr-89: days since randomisation										
n	182	171	166	157	148	137	51	44	37	34
Median	6.0	27.0	49.0	70.0	91.0	112.0	175.0	197.0	217.0	239.5
IQR	2.0–8.0	24.0–30.0	46.0–53.0	67.0–75.0	88.5–96.0	110.0–118.0	169.0–185.0	189.5–207.0	211.0–229.0	232.0–250.0
Docetaxel: total dose (mg)										
n	186	179	169	158	148	128	44	38	34	26
Median	150.0	147.0	145.0	145.0	145.0	145.0	146.5	140.0	142.0	139.5
IQR	140.0–155.0	140.0–152.0	135.0–150.0	130.0–150.0	130.0–150.0	130.0–150.0	130.0–150.0	120.0–150.0	120.0–150.0	120.0–150.0
Docetaxel + ZA: total dose (mg)										
n	180	167	162	155	148	132	57	53	43	34
Median	150.0	150.0	150.0	150.0	148.0	148.0	143.0	142.0	140.0	140.0
IQR	140.0–156.0	140.0–155.0	140.0–155.0	135.0–152.0	130.0–155.0	130.0–155.0	130.0–152.0	130.0–152.0	130.0–150.0	130.0–150.0

Treatment details	Cycle C1 (*N* = 729)		C2 (*N* = 692)		C3 (*N* = 665)		C4 (*N* = 623)		C5 (*N* = 588)		C6 (*N* = 527)		C7 (*N* = 202)		C8 (*N* = 179)		C9 (*N* = 154)		C10 (*N* = 129)	
Docetaxel + Sr-89: total dose (mg)																				
n	181		175		166		152		144		130		49		44		40		35	
Median	150.0		150.0		150.0		150.0		150.0		148.0		150.0		150.0		149.0		150.0	
IQR	140.0–158.0		138.0–156.0		135.0–156.0		135.0–156.0		130.0–156.0		130.0–156.0		130.0–156.0		122.5–156.0		124.5–155.5		120.0–158.0	
Docetaxel + ZA + Sr-89: total dose (mg)																				
n	182		171		166		157		148		137		51		44		37		34	
Median	150.0		150.0		150.0		150.0		150.0		150.0		150.0		150.0		150.0		150.0	
IQR	140.0–155.0		140.0–155.0		135.0–155.0		135.0–155.0		135.0–155.0		135.0–155.0		130.0–150.0		125.0–150.0		135.0–150.0		120.0–150.0	
Treatment details	**C1 (*N* = 729)**		**C2 (*N* = 692)**		**C3 (*N* = 665)**		**C4 (*N* = 623)**		**C5 (*N* = 588)**		**C6 (*N* = 527)**		**C7 (*N* = 202)**		**C8 (*N* = 179)**		**C9 (*N* = 154)**		**C10 (*N* = 129)**	
Score	***n***	**%**	***n***	**%**	***n***	**%**	***n***	**%**	***n***	**%**	***n***	**%**	***n***	**%**	***n***	**%**	***n***	**%**	***n***	**%**
Docetaxel: ECOG performance status score																				
0	70	46.4	65	42.2	51	36.2	53	40.2	52	44.1	40	37.7	14	37.8	12	34.3	10	32.3	8	34.8
1	70	46.4	75	48.7	80	56.7	68	51.5	62	52.5	63	59.4	20	54.1	20	57.1	19	61.3	14	60.9
2	9	6.0	14	9.1	10	7.1	10	7.6	3	2.5	3	2.8	3	8.1	3	8.6	2	6.5	1	4.3
3	2	1.3	0	0.0	0	0.0	1	0.8	1	0.8	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0
Missing	578	–	538	–	524	–	491	–	470	–	421	–	165	–	144	–	123	–	106	–
Docetaxel + ZA: ECOG performance status score																				
0	67	43.8	59	43.1	53	39.8	49	38.0	47	39.5	40	37.4	23	45.1	24	48.0	24	64.9	14	45.2
1	77	50.3	70	51.1	71	53.4	71	55.0	65	54.6	65	60.7	27	52.9	22	44.0	11	29.7	17	54.8
2	9	5.9	8	5.8	8	6.0	8	6.2	7	5.9	2	1.9	1	2.0	4	8.0	2	5.4	0	0.0
3	0	0.0	0	0.0	0	0.0	1	0.8	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0
4	0	0.0	0	0.0	1	0.8	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0
Missing	576	–	555	–	532	–	494	–	469	–	420	–	151	–	129	–	117	–	98	–

continued

TABLE 16 Treatment details by randomisation arm (*continued*)

Treatment details	C1 (*N* = 729)		C2 (*N* = 692)		C3 (*N* = 665)		C4 (*N* = 623)		C5 (*N* = 588)		C6 (*N* = 527)		C7 (*N* = 202)		C8 (*N* = 179)		C9 (*N* = 154)		C10 (*N* = 129)	
Score	*n*	%	*n*	%	*n*	%	*n*	%	*n*	%	*n*	%	*n*	%	*n*	%	*n*	%	*n*	%
Docetaxel + Sr-89: ECOG performance status score																				
0	66	44.3	59	40.4	59	44.4	58	44.3	42	33.6	37	35.2	19	41.3	19	50.0	17	47.2	9	30
1	68	45.6	75	51.4	64	48.1	65	49.6	77	61.6	62	59.0	26	56.5	19	50.0	18	50.0	20	66.7
2	15	10.1	11	7.5	9	6.8	7	5.3	6	4.8	6	5.7	1	2.2	0	0.0	1	2.8	1	3.3
3	0	0.0	1	0.7	1	0.8	1	0.8	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0
Missing	580	–	546	–	532	–	492	–	463	–	422	–	156	–	141	–	118	–	99	–
Docetaxel + ZA + Sr-89: ECOG performance status score																				
0	63	40.4	50	35.7	44	31.0	37	28.7	30	22.9	34	29.6	16	33.3	17	40.5	18	51.4	10	34.5
1	83	53.2	83	59.3	89	62.7	87	67.4	89	67.9	69	60.0	30	62.5	25	59.5	16	45.7	17	58.6
2	9	5.8	7	5.0	8	5.6	4	3.1	10	7.6	12	10.4	2	4.2	0	0.0	1	2.9	2	6.9
3	1	0.6	0	0.0	1	0.7	1	0.8	2	1.5	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0
Missing	573	–	552	–	523	–	494	–	457	–	412	–	154	–	137	–	119	–	100	–
Docetaxel: antibiotics given?																				
No	155	83.8	153	85.5	142	83.5	135	85.4	130	88.4	117	92.1	40	88.9	34	89.5	30	88.2	24	92.3
Yes	30	16.2	26	14.5	28	16.5	23	14.6	17	11.6	10	7.9	5	11.1	4	10.5	4	11.8	2	7.7
Missing	544	–	513	–	495	–	465	–	441	–	400	–	157	–	141	–	120	–	103	–
Docetaxel + ZA: antibiotics given?																				
No	154	85.6	143	85.6	139	85.8	137	88.4	132	89.8	120	90.9	50	87.7	45	84.9	36	83.7	31	91.2
Yes	26	14.4	24	14.4	23	14.2	18	11.6	15	10.2	12	9.1	7	12.3	8	15.1	7	16.3	3	8.8
Missing	549	–	525	–	503	–	468	–	441	–	395	–	145	–	126	–	111	–	95	–
Docetaxel + Sr-89: antibiotics given?																				
No	155	85.6	145	83.3	137	83.5	135	88.8	129	90.2	117	90.0	40	81.6	39	88.6	34	85.0	28	82.4
Yes	26	14.4	29	16.7	27	16.5	17	11.2	14	9.8	13	10.0	9	18.4	5	11.4	6	15.0	6	17.6
Missing	548	–	518	–	501	–	471	–	445	–	397	–	153	–	135	–	114	–	95	–

Treatment details	C1 (*N* = 729)		C2 (*N* = 692)		C3 (*N* = 665)		C4 (*N* = 623)		C5 (*N* = 588)		C6 (*N* = 527)		C7 (*N* = 202)		C8 (*N* = 179)		C9 (*N* = 154)		C10 (*N* = 129)	
Score	*n*	%	*n*	%	*n*	%	*n*	%	*n*	%	*n*	%	*n*	%	*n*	%	*n*	%	*n*	%
Docetaxel + ZA + Sr-89: antibiotics given?																				
No	160	88.9	152	88.9	149	89.8	140	89.2	134	90.5	121	88.3	46	90.2	43	97.7	35	94.6	33	97.1
Yes	20	11.1	19	11.1	17	10.2	17	10.8	14	9.5	16	11.7	5	9.8	1	2.3	2	5.4	1	2.9
Missing	549	–	521	–	499	–	466	–	440	–	390	–	151	–	135	–	117	–	95	–
Docetaxel: analgesics received?																				
No	101	55.2	105	58.7	100	58.8	93	59.2	86	58.5	77	60.6	25	55.6	22	57.9	21	61.8	13	50
Yes	82	44.8	74	41.3	70	41.2	64	40.8	61	41.5	50	39.4	20	44.4	16	42.1	13	38.2	13	50
Missing	546	–	513	–	495	–	466	–	441	–	400	–	157	–	141	–	120	–	103	–
Docetaxel + ZA: analgesics received?																				
No	97	54.5	96	57.5	96	58.9	93	60.4	96	65.3	84	64.1	44	77.2	41	78.8	33	76.7	27	79.4
Yes	81	45.5	71	42.5	67	41.1	61	39.6	51	34.7	47	35.9	13	22.8	11	21.2	10	23.3	7	20.6
Missing	551	–	525	–	502	–	469	–	441	–	396	–	145	–	127	–	111	–	95	–
Docetaxel + Sr-89: analgesics received?																				
No	106	58.6	101	58.0	99	60.4	88	57.9	82	57.7	78	60.5	36	75.0	32	74.4	30	75	24	68.6
Yes	75	41.4	73	42.0	65	39.6	64	42.1	60	42.3	51	39.5	12	25.0	11	25.6	10	25.0	11	31.4
Missing	548	–	518	–	501	–	471	–	446	–	398	–	154	–	136	–	114	–	94	–
Docetaxel + ZA + Sr-89: analgesics received?																				
No	97	53.6	102	59.6	103	62.0	104	66.2	92	62.6	85	63.0	30	58.8	24	54.5	23	62.2	24	72.7
Yes	84	46.4	69	40.4	63	38.0	53	33.8	55	37.4	50	37.0	21	41.2	20	45.5	14	37.8	9	27.3
Missing	548	–	521	–	499	–	466	–	441	–	392	–	151	–	135	–	117	–	96	–
Docetaxel: GCSF received?																				
No	176	95.1	172	96.1	165	97.1	154	97.5	143	97.3	125	98.4	45	100.0	38	100.0	33	97.1	26	100.0
Yes	9	4.9	7	3.9	5	2.9	4	2.5	4	2.7	2	1.6	0	0.0	0	0.0	1	2.9	0	0.0
Missing	544	–	513	–	495	–	465	–	441	–	400	–	157	–	141	–	120	–	103	–

continued

TABLE 16 Treatment details by randomisation arm (*continued*)

Treatment details	C1 (*N* = 729)		C2 (*N* = 692)		C3 (*N* = 665)		C4 (*N* = 623)		C5 (*N* = 588)		C6 (*N* = 527)		C7 (*N* = 202)		C8 (*N* = 179)		C9 (*N* = 154)		C10 (*N* = 129)	
Score	*n*	%	*n*	%	*n*	%	*n*	%	*n*	%	*n*	%	*n*	%	*n*	%	*n*	%	*n*	%
Docetaxel + ZA: GCSF received?																				
No	173	96.1	162	97.0	157	96.3	148	95.5	141	95.9	127	96.2	56	98.2	52	98.1	43	100.0	32	94.1
Yes	7	3.9	5	3.0	6	3.7	7	4.5	6	4.1	5	3.8	1	1.8	1	1.9	0	0.0	2	5.9
Missing	549	–	525	–	502	–	468	–	441	–	395	–	145	–	126	–	111	–	95	–
Docetaxel + Sr-89: GCSF received?																				
No	175	96.7	167	96.0	160	97.6	146	96.1	138	96.5	125	96.2	48	98.0	44	100.0	40	100.0	35	100.0
Yes	6	3.3	7	4.0	4	2.4	6	3.9	5	3.5	5	3.8	1	2.0	0	0.0	0	0.0	0	0.0
Missing	548	–	518	–	501	–	471	–	445	–	397	–	153	–	135	–	114		94	–
Docetaxel + ZA + Sr-89: GCSF received?																				
No	176	97.2	164	95.9	160	96.4	153	97.5	143	96.6	132	96.4	49	96.1	42	95.5	35	94.6	32	94.1
Yes	5	2.8	7	4.1	6	3.6	4	2.5	5	3.4	5	3.6	2	3.9	2	4.5	2	5.4	2	5.9
Missing	548	–	521	–	499	–	466	–	440	–	390	–	151	–	135	–	117	–	95	–
Docetaxel + ZA: reason ZA discontinued																				
GFR increases to > 1.5 ULN	0	0.0	1	20.0	1	25.0	1	25.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0
Hypersensitivity to ZA	0	0.0	1	20.0	1	25.0	1	25.0	1	25.0	1	12.5	1	50.0	1	33.3	0	0.0	0	0.0
Other	4	100.0	3	60.0	2	50.0	2	50.0	3	75.0	7	87.5	1	50.0	2	66.7	3	100.0	2	100.0
Missing	725	–	687	–	661	–	619	–	584	–	519	–	200	–	176	–	151	–	127	–
Docetaxel + ZA + Sr-89: reason ZA discontinued																				
Hypersensitivity to ZA	0	0.0	1	25.0	1	25.0	2	100.0	1	50.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0
Other	2	100.0	3	75.0	3	75.0	0	0.0	1	50.0	4	100.0	1	100.0	3	100.0	0	0.0	2	100.0
Missing	727	–	688	–	661	–	621	–	586	–	523	–	201	–	176	–	154	–	127	–

Treatment details	C1 (*N* = 729)		C2 (*N* = 692)		C3 (*N* = 665)		C4 (*N* = 623)		C5 (*N* = 588)		C6 (*N* = 527)		C7 (*N* = 202)		C8 (*N* = 179)		C9 (*N* = 154)		C10 (*N* = 129)	
Score	*n*	%	*n*	%	*n*	%	*n*	%	*n*	%	*n*	%	*n*	%	*n*	%	*n*	%	*n*	%
Docetaxel + ZA: ZA dose administered (mg)																				
0	2	1.1	5	3.0	4	2.5	5	3.2	3	2.1	8	6.1	2	3.6	3	5.7	3	7.0	2	6.1
3	0	0.0	0	0.0	1	0.6	1	0.6	2	1.4	2	1.5	2	3.6	2	3.8	1	2.3	0	0.0
3.3	7	3.9	5	3.0	5	3.1	6	3.8	3	2.1	7	5.3	1	1.8	1	1.9	1	2.3	2	6.1
3.5	7	3.9	6	3.6	8	4.9	5	3.2	4	2.7	5	3.8	2	3.6	1	1.9	0	0.0	0	0.0
4	164	91.1	151	90.4	145	89.0	139	89.1	134	91.8	110	83.3	49	87.5	46	86.8	38	88.4	29	87.9
Missing	549	–	525	–	502	–	467	–	442	–	395	–	146	–	126	–	111	–	96	–
Docetaxel + ZA + Sr-89: ZA dose administered (mg)																				
0	2	1.1	5	2.9	4	2.4	2	1.3	2	1.4	3	2.2	1	2.0	3	6.8	0	0.0	1	2.9
3	4	2.2	5	2.9	5	3.0	3	1.9	2	1.4	2	1.5	1	2.0	1	2.3	1	2.7	1	2.9
3.3	7	3.8	5	2.9	4	2.4	4	2.5	3	2.0	3	2.2	1	2.0	1	2.3	0	0.0	0	0.0
3.5	8	4.4	6	3.5	6	3.6	5	3.2	5	3.4	2	1.5	2	3.9	1	2.3	1	2.7	2	5.9
4	161	88.5	150	87.7	147	88.6	143	91.1	136	91.9	127	92.7	46	90.2	38	86.4	35	94.6	30	88.2
Missing	547	–	521	–	499	–	466	–	440	–	390	–	151	–	135	–	117	–	95	–

GCSF, granulocyte colony-stimulating factor; GFR, glomerular filtration rate; ULN, upper limit of normal.

TABLE 17 Treatment details by comparison groups

	Cycle									
Treatment details	**C1**	**C2**	**C3**	**C4**	**C5**	**C6**	**C7**	**C8**	**C9**	**C10**
No ZA: days since randomisation										
n	367	354	336	310	292	258	94	82	74	61
Median	6.0	28.0	49.0	70.0	91.0	113.0	167.5	189.0	210.0	232.0
IQR	2.0–9.0	24.0–31.0	46.0–53.0	67.0–76.0	89.0–97.0	110.0–118.0	134.0–175.0	155.0–196.0	176.0–220.0	197.0–244.0
ZA: days since randomisation										
n	362	338	329	313	296	269	108	97	80	68
Median	6.0	27.0	49.0	70.0	91.0	112.0	145.0	164.0	189.5	215.0
IQR	2.0–9.0	24.0–31.0	46.0–53.0	67.0–75.0	88.0–96.0	110.0–118.0	134.0–175.0	155.0–196.0	177.0–217.0	198.5–239.5
No Sr-89: days since randomisation										
n	366	346	333	314	296	260	102	91	77	60
Median	6.0	27.0	49.0	70.0	91.0	112.0	134.0	155.0	177.0	197.0
IQR	2.0–9.0	24.0–31.0	45.0–53.0	67.0–76.0	88.0–97.0	110.0–119.0	131.0–140.0	151.0–162.0	173.0–183.0	194.0–203.5
Sr-89: days since randomisation										
n	363	346	332	309	292	267	100	88	77	69
Median	6.0	28.0	49.0	70.0	91.0	113.0	175.0	196.0	217.0	240.0
IQR	3.0–9.0	24.0–30.0	46.0–53.0	67.0–75.0	89.0–96.0	110.0–118.0	169.0–184.0	190.0–206.0	212.0–229.0	233.0–251.0
No ZA: total dose (mg)										
n	367	354	335	310	292	258	93	82	74	61
Median	150.0	149.0	147.0	145.0	145.0	145.0	148.0	148.0	148.0	140.0
IQR	140.0–155.0	140.0–155.0	135.0–155.0	135.0–155.0	130.0–155.0	130.0–155.0	130.0–155.0	120.0–155.0	124.0–155.0	120.0–155.0

Treatment details	Cycle C1	C2	C3	C4	C5	C6	C7	C8	C9	C10
ZA: total dose (mg)										
n	362	338	328	312	296	269	108	97	80	68
Median	150.0	150.0	150.0	150.0	150.0	150.0	145.0	145.0	146.5	144.0
IQR	140.0–155.0	140.0–155.0	135.5–155.0	135.0–153.5	135.0–155.0	135.0–155.0	130.0–150.0	130.0–150.0	130.0–150.0	127.0–150.0
No Sr-89: total dose (mg)										
n	366	346	331	313	296	260	101	91	77	60
Median	150.0	150.0	150.0	145.0	145.0	145.0	144.0	140.0	140.0	140.0
IQR	140.0–155.0	140.0–155.0	135.0–152.0	135.0–152.0	130.0–152.0	130.0–151.0	130.0–150.0	130.0–152.0	130.0–150.0	120.0–150.0
Sr-89: total dose (mg)										
n	363	346	332	309	292	267	100	88	77	69
Median	150.0	150.0	150.0	150.0	150.0	150.0	150.0	150.0	150.0	150.0
IQR	140.0– 155.0	140.0–155.0	135.0–155.0	135.0–155.0	135.0–155.0	130.0–155.0	130.0–150.0	122.5–152.5	130.0–150.0	120.0–155.0

Treatment details	C1		C2		C3		C4		C5		C6		C7		C8		C9		C10	
Score	*n*	%	*n*	%	*n*	%	*n*	%	*n*	%	*n*	%	*n*	%	*n*	%	*n*	%	*n*	%
No ZA: ECOG performance status score																				
0	136	45.3	124	41.3	110	40.1	111	42.2	94	38.7	77	36.5	33	39.8	31	42.5	27	40.3	17	32.1
1	138	46.0	150	50.0	144	52.6	133	50.6	139	57.2	125	59.2	46	55.4	39	53.4	37	55.2	34	64.2
2	24	8.0	25	8.3	19	6.9	17	6.5	9	3.7	9	4.3	4	4.8	3	4.1	3	4.5	2	3.8
3	2	0.7	1	0.3	1	0.4	2	0.8	1	0.4	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0

continued

TABLE 17 Treatment details by comparison groups (*continued*)

Treatment details	C1		C2		C3		C4		C5		C6		C7		C8		C9		C10	
Score	*n*	%	*n*	%	*n*	%	*n*	%	*n*	%	*n*	%	*n*	%	*n*	%	*n*	%	*n*	%
ZA: ECOG performance status score																				
0	130	42.1	109	39.4	97	35.3	86	33.3	77	30.8	74	33.3	39	39.4	41	44.6	42	58.3	24	40.0
1	160	51.8	153	55.2	160	58.2	158	61.2	154	61.6	134	60.4	57	57.6	47	51.1	27	37.5	34	56.7
2	18	5.8	15	5.4	16	5.8	12	4.7	17	6.8	14	6.3	3	3.0	4	4.3	3	4.2	2	3.3
3	1	0.3	0	0.0	1	0.4	2	0.8	2	0.8	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0
4	0	0.0	0	0.0	1	0.4	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0
No Sr-89: ECOG performance status score																				
0	137	45.1	124	42.6	104	38.0	102	39.1	99	41.8	80	37.6	37	42.0	36	42.4	34	50.0	22	40.7
1	147	48.4	145	49.8	151	55.1	139	53.3	127	53.6	128	60.1	47	53.4	42	49.4	30	44.1	31	57.4
2	18	5.9	22	7.6	18	6.6	18	6.9	10	4.2	5	2.3	4	4.5	7	8.2	4	5.9	1	1.9
3	2	0.7	0	0.0	0	0.0	2	0.8	1	0.4	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0
4	0	0.0	0	0.0	1	0.4	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0
Sr-89: ECOG performance status score																				
0	129	42.3	109	38.1	103	37.5	95	36.5	72	28.1	71	32.3	35	37.2	36	45.0	35	49.3	19	32.2
1	151	49.5	158	55.2	153	55.6	152	58.5	166	64.8	131	59.5	56	59.6	44	55.0	34	47.9	37	62.7
2	24	7.9	18	6.3	17	6.2	11	4.2	16	6.3	18	8.2	3	3.2	0	0.0	2	2.8	3	5.1
3	1	0.3	1	0.3	2	0.7	2	0.8	2	0.8	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0
No ZA: antibiotics given?																				
No	310	84.7	298	84.4	279	83.5	270	87.1	259	89.3	234	91.1	80	85.1	73	89.0	64	86.5	52	86.7
Yes	56	15.3	55	15.6	55	16.5	40	12.9	31	10.7	23	8.9	14	14.9	9	11.0	10	13.5	8	13.3

Treatment details	C1		C2		C3		C4		C5		C6		C7		C8		C9		C10	
Score	***n***	**%**	***n***	**%**	***n***	**%**	***n***	**%**	***n***	**%**	***n***	**%**	***n***	**%**	***n***	**%**	***n***	**%**	***n***	**%**
ZA: antibiotics given?																				
No	314	87.2	295	87.3	288	87.8	277	88.8	266	90.2	241	89.6	96	88.9	88	90.7	71	88.8	64	94.1
Yes	46	12.8	43	12.7	40	12.2	35	11.2	29	9.8	28	10.4	12	11.1	9	9.3	9	11.3	4	5.9
No Sr-89: antibiotics given?																				
No	309	84.7	296	85.5	281	84.6	272	86.9	262	89.1	237	91.5	90	88.2	79	86.8	66	85.7	55	91.7
Yes	56	15.3	50	14.5	51	15.4	41	13.1	32	10.9	22	8.5	12	11.8	12	13.2	11	14.3	5	8.3
Sr-89: antibiotics given?																				
No	315	87.3	297	86.1	286	86.7	275	89.0	263	90.4	238	89.1	86	86.0	82	93.2	69	89.6	61	89.7
Yes	46	12.7	48	13.9	44	13.3	34	11.0	28	9.6	29	10.9	14	14.0	6	6.8	8	10.4	7	10.3
No ZA: analgesics received?																				
No	207	56.9	206	58.4	199	59.6	181	58.6	168	58.1	155	60.5	61	65.6	54	66.7	51	68.9	37	60.7
Yes	157	43.1	147	41.6	135	40.4	128	41.4	121	41.9	101	39.5	32	34.4	27	33.3	23	31.1	24	39.3
ZA: analgesics received?																				
No	194	54.0	198	58.6	199	60.5	197	63.3	188	63.9	169	63.5	74	68.5	65	67.7	56	70.0	51	76.1
Yes	165	46.0	140	41.4	130	39.5	114	36.7	106	36.1	97	36.5	34	31.5	31	32.3	24	30.0	16	23.9
No Sr-89: analgesics received?																				
No	198	54.8	201	58.1	196	58.9	186	59.8	182	61.9	161	62.4	69	67.6	63	70.0	54	70.1	40	66.7
Yes	163	45.2	145	41.9	137	41.1	125	40.2	112	38.1	97	37.6	33	32.4	27	30.0	23	29.9	20	33.3
Sr-89: analgesics received?																				
No	203	56.1	203	58.8	202	61.2	192	62.1	174	60.2	163	61.7	66	66.7	56	64.4	53	68.8	48	70.6
Yes	159	43.9	142	41.2	128	38.8	117	37.9	115	39.8	101	38.3	33	33.3	31	35.6	24	31.2	20	29.4

continued

TABLE 17 Treatment details by comparison groups (*continued*)

Treatment details	C1		C2		C3		C4		C5		C6		C7		C8		C9		C10	
Score	*n*	%	*n*	%	*n*	%	*n*	%	*n*	%	*n*	%	*n*	%	*n*	%	*n*	%	*n*	%
No ZA: GCSF received?																				
No	351	95.9	339	96.0	325	97.3	300	96.8	281	96.9	250	97.3	93	98.9	82	100.0	73	98.6	61	100.0
Yes	15	4.1	14	4.0	9	2.7	10	3.2	9	3.1	7	2.7	1	1.1	0	0.0	1	1.4	0	0.0
ZA: GCSF received?																				
No	349	96.7	326	96.4	317	96.4	301	96.5	284	96.3	259	96.3	105	97.2	94	96.9	78	97.5	64	94.1
Yes	12	3.3	12	3.6	12	3.6	11	3.5	11	3.7	10	3.7	3	2.8	3	3.1	2	2.5	4	5.9
No Sr-89: GCSF received?																				
No	349	95.6	334	96.5	322	96.7	302	96.5	284	96.6	252	97.3	101	99.0	90	98.9	76	98.7	58	96.7
Yes	16	4.4	12	3.5	11	3.3	11	3.5	10	3.4	7	2.7	1	1.0	1	1.1	1	1.3	2	3.3
Sr-89: GCSF received?																				
No	351	97.0	331	95.9	320	97.0	299	96.8	281	96.6	257	96.3	97	97.0	86	97.7	75	97.4	67	97.1
Yes	11	3.0	14	4.1	10	3.0	10	3.2	10	3.4	10	3.7	3	3.0	2	2.3	2	2.6	2	2.9
ZA: reason ZA discontinued																				
GFR increases to > 1.5 ULN	0	0.0	1	11.1	1	12.5	1	16.7	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0
Hypersensitivity to ZA	0	0.0	2	22.2	2	25.0	3	50.0	2	33.3	1	8.3	1	33.3	1	16.7	0	0.0	0	0.0
Other	6	100.0	6	66.7	5	62.5	2	33.3	4	66.7	11	91.7	2	66.7	5	83.3	3	100.0	4	100.0
No Sr-89: reason ZA discontinued																				
GFR increases to > 1.5 ULN	0	0.0	1	20.0	1	25.0	1	25.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0
Hypersensitivity to ZA	0	0.0	1	20.0	1	25.0	1	25.0	1	25.0	1	12.5	1	50.0	1	33.3	0	0.0	0	0.0
Other	4	100.0	3	60.0	2	50.0	2	50.0	3	75.0	7	87.5	1	50.0	2	66.7	3	100.0	2	100.0

Treatment details	C1		C2		C3		C4		C5		C6		C7		C8		C9		C10	
Score	*n*	%	*n*	%	*n*	%	*n*	%	*n*	%	*n*	%	*n*	%	*n*	%	*n*	%	*n*	%
Sr-89: reason ZA discontinued																				
Hypersensitivity to ZA	0	0.0	1	25.0	1	25.0	2	100.0	1	50.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0
Other	2	100.0	3	75.0	3	75.0	0	0.0	1	50.0	4	100.0	1	100.0	3	100.0	0	0.0	2	100.0
ZA: ZA dose administered (mg)																				
0	4	1.1	10	3.0	8	2.4	7	2.2	5	1.7	11	4.1	3	2.8	6	6.2	3	3.8	3	4.5
3	4	1.1	5	1.5	6	1.8	4	1.3	4	1.4	4	1.5	3	2.8	3	3.1	2	2.5	1	1.5
3.3	14	3.9	10	3.0	9	2.7	10	3.2	6	2.0	10	3.7	2	1.9	2	2.1	1	1.3	2	3.0
3.5	15	4.1	12	3.6	14	4.3	10	3.2	9	3.1	7	2.6	4	3.7	2	2.1	1	1.3	2	3.0
4	325	89.8	301	89.1	292	88.8	282	90.1	270	91.8	237	88.1	95	88.8	84	86.6	73	91.3	59	88.1
No Sr-89: ZA dose administered (mg)																				
0	2	1.1	5	3.0	4	2.5	5	3.2	3	2.1	8	6.1	2	3.6	3	5.7	3	7.0	2	6.1
3	0	0.0	0	0.0	1	0.6	1	0.6	2	1.4	2	1.5	2	3.6	2	3.8	1	2.3	0	0.0
3.3	7	3.9	5	3.0	5	3.1	6	3.8	3	2.1	7	5.3	1	1.8	1	1.9	1	2.3	2	6.1
3.5	7	3.9	6	3.6	8	4.9	5	3.2	4	2.7	5	3.8	2	3.6	1	1.9	0	0.0	0	0.0
4	164	91.1	151	90.4	145	89.0	139	89.1	134	91.8	110	83.3	49	87.5	46	86.8	38	88.4	29	87.9
Sr-89: ZA dose administered (mg)																				
0	2	1.1	5	2.9	4	2.4	2	1.3	2	1.4	3	2.2	1	2.0	3	6.8	0	0.0	1	2.9
3	4	2.2	5	2.9	5	3.0	3	1.9	2	1.4	2	1.5	1	2.0	1	2.3	1	2.7	1	2.9
3.3	7	3.8	5	2.9	4	2.4	4	2.5	3	2.0	3	2.2	1	2.0	1	2.3	0	0.0	0	0.0
3.5	8	4.4	6	3.5	6	3.6	5	3.2	5	3.4	2	1.5	2	3.9	1	2.3	1	2.7	2	5.9
4	161	88.5	150	87.7	147	88.6	143	91.1	136	91.9	127	92.7	46	90.2	38	86.4	35	94.6	30	88.2

GCSF, granulocyte colony-stimulating factor; GFR, glomerular filtration rate; ULN, upper limit of normal.

TABLE 18 Other reasons for ZA discontinuation

Other reasons	Number of patients
Hypocalcaemia	6
Breathlessness	1
Clinical decision	6
Dental treatment	10
Raised creatinine	3
Anaemia	1
Osteonecrosis	1
Patient choice	1
Unspecified side effects	2
Toxicities	9
Ulcer on gums	1
Omitted in error	4
Hypophosphataemia	1
Investigation of jaw pain	1

Delivery of strontium-89

Table 19 shows the timings of delivery and dose of Sr-89 administered for the 253 patients who received Sr-89 split firstly by randomisation arm and then by comparison groups. Reasons for not receiving Sr-89 are detailed in withdrawal Sr-89 section.

Tables 20 and *21* show that most patients who were able to receive Sr-89 received the total dose, independent of whether or not they were randomised to also receive ZA.

TABLE 19 Strontium-89 administration by randomisation arm

Sr-89 details	Randomisation arm		Comparison group
	Docetaxel + Sr-89 ($N = 123$)	Docetaxel + ZA + Sr-89 ($N = 130$)	All patients receiving Sr-89 ($N = 253$)
Days from randomisation to Sr-89			
n	123	130	253
Median	144.0	145.5	145.0
IQR	140.0–149.0	140.0–152.0	140.0–151.0
Range	132.0–203.0	133.0–182.0	132.0–203.0
Sr-89 dose (MBq)			
n	123	130	253
Median	150.0	150.0	150.0
IQR	150.0–150.0	149.0–150.0	150.0–150.0
Range	89.0–165.0	89.0–169.0	89.0–169.0

TABLE 20 Docetaxel dose reductions cycles 1–5

	C1 (*N* = 729)		C2 (*N* = 692)		C3 (*N* = 665)		C4 (*N* = 623)		C5 (*N* = 588)	
Dose reduction details	***n***	**%**	***n***	**%**	***n***	**%**	***n***	**%**	***n***	**%**
Did the patient have a dose reduction?										
No	723	99.2	627	90.6	625	94.0	579	92.9	550	93.9
Yes	6	0.8	65	9.4	40	6.0	44	7.1	36	6.1
Missing	0	–	0	–	0	–	0	–	2	–
Split by randomisation arm *Docetaxel: was the dose reduced?*										
No	184	98.9	164	91.6	161	94.7	142	89.9	136	92.5
Yes	2	1.1	15	8.4	9	5.3	16	10.1	11	7.5
Docetaxel + ZA: was the dose reduced?										
No	180	100.0	148	88.6	153	93.9	147	94.2	139	94.6
Yes	0	0.0	19	11.4	10	6.1	9	5.8	8	5.4
Docetaxel + Sr-89: was the dose reduced?										
No	178	98.3	157	89.7	156	94.0	145	95.4	136	94.4
Yes	3	1.7	18	10.3	10	6.0	7	4.6	8	5.6
Docetaxel + ZA + Sr-89: was the dose reduced?										
No	181	99.5	158	92.4	155	93.4	145	92.4	139	93.9
Yes	1	0.5	13	7.6	11	6.6	12	7.6	9	6.1
Docetaxel: reasons for reduction										
Non-study drug related	0	0.0	2	13.3	0	0.0	1	6.3	0	0.0
Study drug-related haematological toxicity	1	50.0	9	60.0	6	66.7	8	50.0	5	45.5
Study drug-related non-haematological toxicity	0	0.0	2	13.3	0	0.0	2	12.5	5	45.5
Study drug-related both	0	0.0	1	6.7	0	0.0	0	0.0	1	9.1
Study drug-related other, specify	1	50.0	1	6.7	3	33.3	5	31.3	0	0.0
Docetaxel + ZA: reasons for reduction										
Non-study drug related	0	0.0	1	5.3	1	10.0	1	11.1	0	0.0
Study drug-related haematological toxicity	0	0.0	8	42.1	5	50.0	5	55.6	1	12.5
Study drug-related non-haematological toxicity	0	0.0	2	10.5	2	20.0	1	11.1	5	62.5
Study drug-related both	0	0.0	4	21.1	1	10.0	1	11.1	1	12.5
Study drug-related other, specify	0	0.0	4	21.1	1	10.0	1	11.1	1	12.5
Docetaxel + Sr-89: reasons for reduction										
Non-study drug related	0	0.0	1	5.6	0	0.0	0	0.0	0	0.0
Study drug-related haematological toxicity	0	0.0	10	55.6	5	50.0	3	42.9	4	50.0
Study drug-related non-haematological toxicity	0	0.0	3	16.7	3	30.0	3	42.9	1	12.5
Study drug-related both	1	33.3	3	16.7	1	10.0	1	14.3	1	12.5
Study drug-related other, specify	2	66.7	1	5.6	1	10.0	0	0.0	2	25.0
Docetaxel + ZA + Sr-89: reasons for reduction										
Non-study drug related	0	0.0	1	7.7	1	9.1	2	16.7	1	11.1
Study drug-related haematological toxicity	1	100.0	9	69.2	7	63.6	5	41.7	4	44.4
Study drug-related non-haematological toxicity	0	0.0	2	15.4	2	18.2	2	16.7	2	22.2
Study drug-related other, specify	0	0.0	1	7.7	1	9.1	3	25.0	2	22.2

TABLE 21 Docetaxel dose reductions cycles 6–10

	C6 (*N* = 527)		C7 (*N* = 202)		C8 (*N* = 179)		C9 (*N* = 154)		C10 (*N* = 129)	
Dose reduction details	***n***	**%**	***n***	**%**	***n***	**%**	***n***	**%**	***n***	**%**
Did the patient have a dose reduction?										
No	493	93.7	191	94.6	162	90.5	147	95.5	120	93.8
Yes	33	6.3	11	5.4	17	9.5	7	4.5	8	6.3
Missing	1		0		0		0		1	
Split by randomisation arms *Docetaxel: was the dose reduced*										
No	121	94.5	42	93.3	32	84.2	32	94.1	23	88.5
Yes	7	5.5	3	6.7	6	15.8	2	5.9	3	11.5
Docetaxel + ZA: was the dose reduced?										
No	123	93.9	53	93.0	51	96.2	42	97.7	31	91.2
Yes	8	6.1	4	7.0	2	3.8	1	2.3	3	8.8
Docetaxel + Sr-89: was the dose reduced?										
No	123	94.6	46	93.9	40	90.9	38	95.0	34	100.0
Yes	7	5.4	3	6.1	4	9.1	2	5.0	0	0.0
Docetaxel + ZA + Sr-89: was the dose reduced?										
No	126	92.0	50	98.0	39	88.6	35	94.6	32	94.1
Yes	11	8.0	1	2	5	11.4	2	5.4	2	5.9
Docetaxel: reasons for reduction										
Study drug-related haematological toxicity	4	57.1	2	66.7	2	33.3	0	0.0	0	0.0
Study drug-related non-haematological toxicity	1	14.3	1	33.3	4	66.7	2	100.0	3	100.0
Study drug-related both	2	28.6	0	0.0	0	0.0	0	0.0	0	0.0
Docetaxel + ZA: reasons for reduction										
Non-study drug related	1	14.3	0	0.0	0	0.0	0	0.0	0	0.0
Study drug-related haematological toxicity	3	42.9	1	25.0	1	50.0	0	0.0	2	66.7
Study drug-related non-haematological toxicity	2	28.6	2	50.0	0	0.0	1	100.0	1	33.3
Study drug-related other, specify	1	14.3	1	25.0	1	50.0	0	0.0	0	0.0
Docetaxel + Sr-89: reasons for reduction										
Non-study drug related	0	0.0	1	33.3	0	0.0	0	0.0	0	0.0
Study drug-related haematological toxicity	3	42.9	0	0.0	1	25.0	1	50.0	0	0.0
Study drug-related non-haematological toxicity	2	28.6	1	33.3	1	25.0	1	50.0	0	0.0
Study drug-related both	1	14.3	1	33.3	1	25.0	0	0.0	0	0.0
Study drug-related other, specify	1	14.3	0	0.0	1	25.0	0	0.0	0	0.0
Docetaxel + ZA + Sr-89: reasons for reduction										
Non-study drug related	2	18.2	0	0.0	0	0.0	0	0.0	0	0.0
Study drug-related haematological toxicity	4	36.4	1	100.0	3	60.0	1	50.0	1	50.0
Study drug-related non-haematological toxicity	4	36.4	0	0.0	2	40.0	1	50.0	1	50.0
Study drug-related other, specify	1	9.1	0	0.0	0	0.0	0	0.0	0	0.0

Dose intensity

The protocol-defined starting dose of docetaxel was 75 mg/m^2 (up to a maximum dose of 165 mg). *Figures 9* and *10*, split by comparisons, show the actual dose of docetaxel received (lines) and the numbers of patients off-treatment (bar) over the 10 cycles of the trial.

The graphs show that there were only minimal changes in the total doses of docetaxel given during the course of the trial.

Dose reductions and delays

Reductions

Table 20 shows the number of and reasons for dose reductions by randomisation arm over time for cycles 1–5 and *Table 21* for cycles 6–10. In total, 267 dose reductions were reported across all 10 cycles, which equated to 6% of all for docetaxel cycles given being reduced.

Delays

Table 22 shows the numbers of docetaxel delays over time and by randomisation arm for cycles 1–5 and *Table 23* for cycles 6–10. In total, there were 297 delays reported, equating to delays in 7% of all docetaxel cycles received.

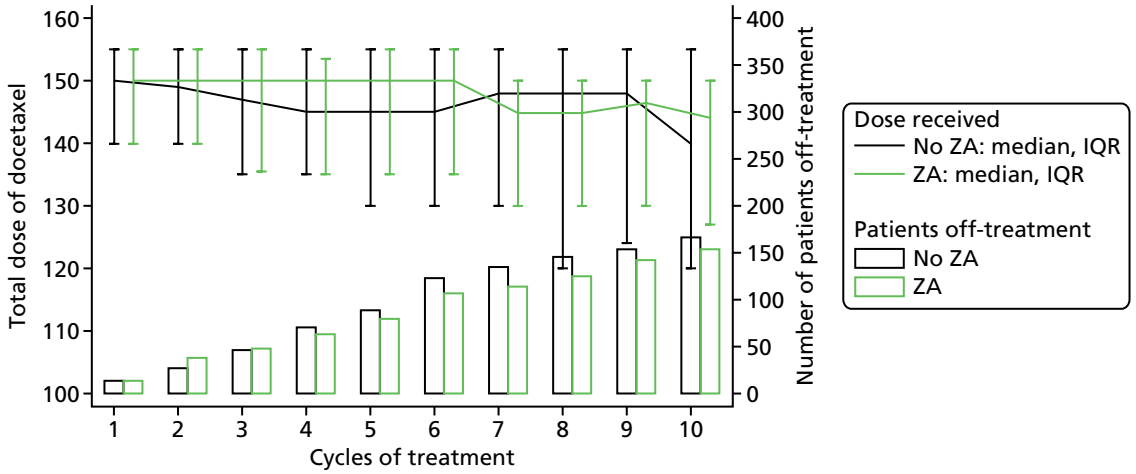


FIGURE 9 Docetaxel administration by ZA comparison.

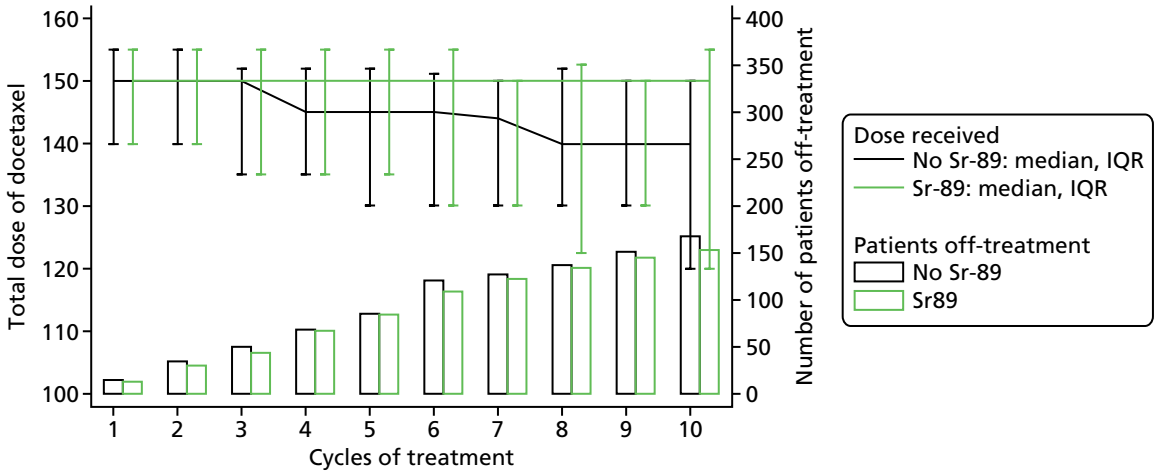


FIGURE 10 Docetaxel administration by Sr-89 comparison.

TABLE 22 Docetaxel dose delays for cycles 1–5

	C1 (*N* = 729)		C2 (*N* = 692)		C3 (*N* = 665)		C4 (*N* = 623)		C5 (*N* = 588)	
Dose delay details	***n***	**%**	***n***	**%**	***n***	**%**	***n***	**%**	***n***	**%**
Did the patient have a dose delay?										
No	712	97.7	637	92.1	617	92.8	571	91.7	545	92.8
Yes	17	2.3	55	7.9	48	7.2	52	8.3	42	7.2
Missing	0		0		0		0		1	
Split by randomisation arm *Docetaxel: was cycle delayed?*										
No	183	98.4	163	91.1	158	92.9	144	91.1	134	90.5
Yes	3	1.6	16	8.9	12	7.1	14	8.9	14	9.5
Docetaxel + ZA: was cycle delayed?										
No	177	98.3	154	92.2	152	93.3	140	89.7	136	92.5
Yes	3	1.7	13	7.8	11	6.7	16	10.3	11	7.5
Docetaxel + Sr-89: was cycle delayed?										
No	173	95.6	162	92.6	155	93.4	142	93.4	133	92.4
Yes	8	4.4	13	7.4	11	6.6	10	6.6	11	7.6
Docetaxel + ZA + Sr-89: was cycle delayed?										
No	179	98.4	158	92.4	152	91.6	145	92.4	142	95.9
Yes	3	1.6	13	7.6	14	8.4	12	7.6	6	4.1
Docetaxel: reasons for delay										
Non-study drug related	0	0.0	4	25.0	3	27.3	2	14.3	7	50.0
Study drug-related haematological toxicity	0	0.0	4	25.0	1	9.1	2	14.3	0	0.0
Study drug-related non-haematological toxicity	0	0.0	1	6.3	1	9.1	2	14.3	2	14.3
Study drug-related other, specify	3	100.0	7	43.8	6	54.5	8	57.1	5	35.7
Docetaxel + ZA: reasons for delay										
Non-study drug related	2	66.7	0	0.0	1	9.1	6	37.5	2	18.2
Study drug-related haematological toxicity	0	0.0	3	23.1	3	27.3	3	18.8	1	9.1
Study drug-related non-haematological toxicity	0	0.0	3	23.1	3	27.3	1	6.3	3	27.3
Study drug-related both	0	0.0	2	15.4	0	0.0	0	0.0	0	0.0
Study drug-related other, specify	1	33.3	5	38.5	4	36.4	6	37.5	5	45.5
Docetaxel + Sr-89: reasons for delay										
Non-study drug related	3	37.5	0	0.0	0	0.0	2	20.0	2	18.2
Study drug-related haematological toxicity	0	0.0	5	38.5	2	18.2	0	0.0	2	18.2
Study drug-related non-haematological toxicity	0	0.0	0	0.0	3	27.3	3	30.0	1	9.1
Study drug-related both	0	0.0	2	15.4	1	9.1	1	10.0	0	0.0
Study drug-related other, specify	5	62.5	6	46.2	5	45.5	4	40.0	6	54.5
Docetaxel + ZA + Sr-89: reasons for delay										
Non-study drug related	2	66.7	2	15.4	1	7.1	2	16.7	2	33.3
Study drug-related haematological toxicity	0	0.0	5	38.5	1	7.1	1	8.3	0	0.0
Study drug-related non-haematological toxicity	0	0.0	3	23.1	3	21.4	4	33.3	0	0.0
Study drug-related both	0	0.0	0	0.0	0	0.0	0	0.0	1	16.7
Study drug-related other, specify	1	33.3	3	23.1	9	64.3	5	41.7	3	50.0

TABLE 23 Docetaxel dose delays for cycles 6–10

	C6 (*N* = 527)		C7 (*N* = 202)		C8 (*N* = 179)		C9 (*N* = 154)		C10 (*N* = 129)	
Dose delay details	***n***	**%**	***n***	**%**	***n***	**%**	***n***	**%**	***n***	**%**
Did the patient have a dose delay?										
No	493	93.5	182	90.1	162	90.5	145	94.2	125	97.7
Yes	34	6.5	20	9.9	17	9.5	9	5.8	3	2.3
Missing	0		0		0		0		1	
Split by randomisation arm *Docetaxel: was cycle delayed?*										
No	125	97.7	43	95.6	35	92.1	34	100.0	25	96.2
Yes	3	2.3	2	4.4	3	7.9	0	0.0	1	3.8
Docetaxel + ZA: was cycle delayed?										
No	121	91.7	52	91.2	49	92.5	40	93.0	33	97.1
Yes	11	8.3	5	8.8	4	7.5	3	7.0	1	2.9
Docetaxel + Sr-89: was cycle delayed?										
No	118	90.8	43	87.8	39	88.6	35	87.5	33	97.1
Yes	12	9.2	6	12.2	5	11.4	5	12.5	1	2.9
Docetaxel + ZA + Sr-89: was cycle delayed?										
No	129	94.2	44	86.3	39	88.6	36	97.3	34	100.0
Yes	8	5.8	7	13.7	5	11.4	1	2.7	0	0.0
Docetaxel: reasons for delay										
Non-study drug related	1	33.3	1	50.0	1	33.3	0	0.0	0	0.0
Study drug-related non-haematological toxicity	0	0.0	0	0.0	1	33.3	0	0.0	0	0.0
Study drug-related other, specify	2	66.7	1	50.0	1	33.3	0	0.0	1	100.0
Docetaxel + ZA: reasons for delay										
Non-study drug related	3	27.3	2	40.0	0	0.0	0	0.0	0	0.0
Study drug-related haematological toxicity	2	18.2	0	0.0	0	0.0	0	0.0	0	0.0
Study drug-related non-haematological toxicity	0	0.0	2	40.0	2	50.0	0	0.0	0	0.0
Study drug-related other, specify	6	54.5	1	20.0	2	50.0	3	100.0	1	100.0
Docetaxel + Sr-89: reasons for delay										
Non-study drug related	2	16.7	1	16.7	0	0.0	1	20.0	0	0.0
Study drug-related haematological toxicity	0	0.0	0	0.0	1	20.0	0	0.0	0	0.0
Study drug-related non-haematological toxicity	4	33.3	0	0.0	0	0.0	0	0.0	0	0.0
Study drug-related both	0	0.0	0	0.0	1	20.0	0	0.0	0	0.0
Study drug-related other, specify	6	50.0	5	83.3	3	60.0	4	80.0	1	100.0
Docetaxel + ZA + Sr-89: reasons for delay										
Non-study drug related	3	37.5	1	14.3	2	40.0	0	0.0	0	0.0
Study drug-related haematological toxicity	0	0.0	0	0.0	1	20.0	0	0.0	0	0.0
Study drug-related non-haematological toxicity	1	12.5	0	0.0	1	20.0	0	0.0	0	0.0
Study drug-related both	1	12.5	0	0.0	0	0.0	0	0.0	0	0.0
Study drug-related other, specify	3	37.5	6	85.7	1	20.0	1	100.0	0	0.0

Figures 11 and *12* show the overall (line) dose reductions and delays, and the reasons (bar) for these, as a percentage of the number of patients who received each cycle. *Figure 11* was split by Sr-89 and *Figure 12* by ZA.

It is clear in both figures that study drug-related haematological toxicities tended to result in dose reductions rather than delays. For patients receiving Sr-89 there appeared to be a peak in delays to cycle 7 following Sr-89 admission, this fits with a drop in the percentage of patients needing dose reductions at that cycle.

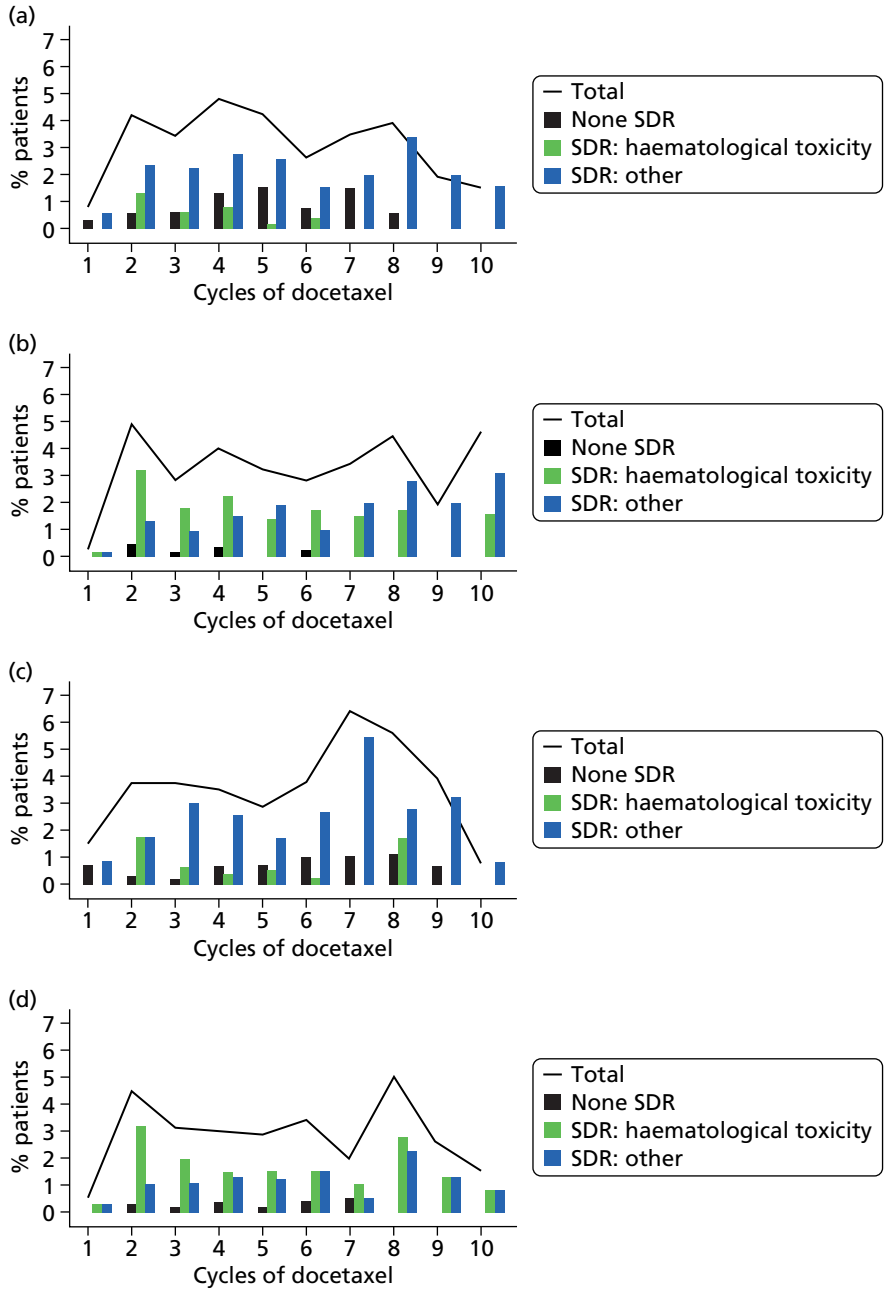


FIGURE 11 Reasons for docetaxel reductions and delays by Sr-89. SDR, study-related drug. (a) No Sr-89: delays; (b) no Sr-89: reductions; (c) Sr-89:delays; and (d) Sr-89: reductions.

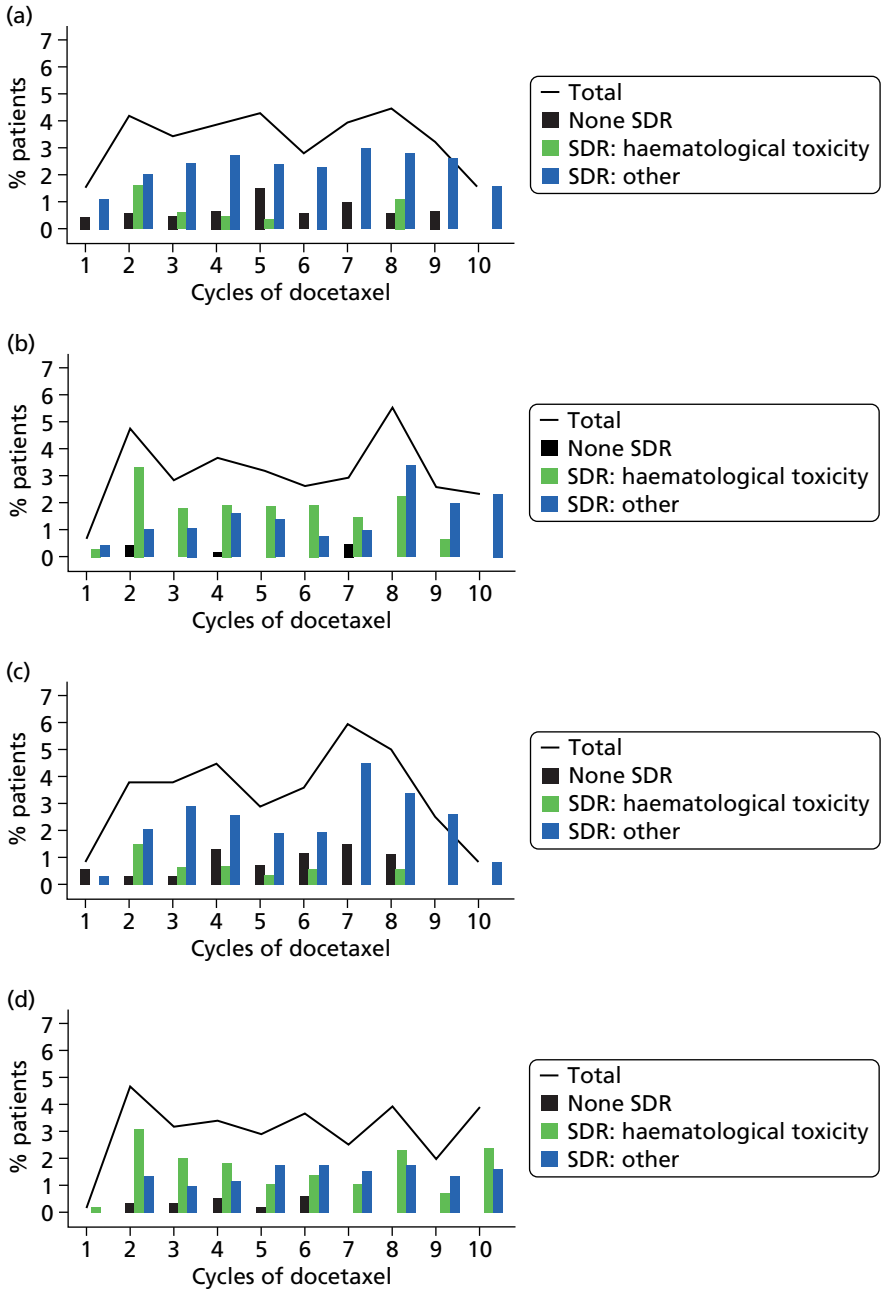


FIGURE 12 Reasons for docetaxel reductions and delays by ZA. SDR, study-related drug. (a) No ZA: delays; (b) no ZA: reductions; (c) ZA: delays; and (d) ZA: reductions.

Concomitant medications

Concomitant medications were collected at randomisation and during treatment visits. In addition, all concomitant medications given in response to serious adverse events (SAEs) were recorded on the SAE form. At the point of tumour, pain or PSA progression, sites were specifically asked about radiotherapy, radioisotopes and bisphosphonates and given the option to record any other treatments provided at that time.

In total, 9637 concomitant medications were reported, of which 2152 (22%) were related to concomitant medications that were already being taken at randomisation. The majority, 5233 (54%), were taken prior to the patient experiencing CPFS, and 1969 (20%) were taken following CPFS. In addition to this, in the case of 304 (3%) concomitant medications, the date on which they were taken was unavailable.

Details of all concomitant medications reported by more than 20 patients can be found in *Appendix 5*, *Tables 82–87*, split by both randomisation arm and comparison groups. The data within these tables are also split by whether the concomitant medications were administered at baseline, post baseline but prior to CPFS or following CPFS.

Analgesic concomitant medications

Patients were asked to complete pain diaries for the 7 days prior to each visit. Patients were asked to list all pain medication taken during these days. This does not give a complete overview of analgesic use; however, as recording was the same in all arms, any difference should be representative of overall use.

In total, 40,029 instances of receiving analgesic medications were reported by 575 patients; 19,494 (79%) were opioid analgesics and 20,535 (51%) non-opioid. These were evenly distributed both between randomisation arms and across comparison groups; details are presented in *Tables 24* and *25*.

Details of the types of analgesic medications being taken can be found in *Appendix 5*, *Tables 88–93*, split by both randomisation arm and comparison groups. The data within these tables are also split by whether the concomitant medication was administered at baseline, post baseline but prior to CPFS or following CPFS.

TABLE 24 Opioid vs. non-opioid analgesic medications split by randomisation arms

Analgesic	Docetaxel	Docetaxel + ZA	Docetaxel + Sr-89	Docetaxel + ZA + Sr-89	Overall
Number of patients					
Non-opioid	87	82	88	90	347
Opioid	59	64	5	44	225
Missing	1	1	1	0	3
Number of instances					
Non-opioid	5203	5106	5188	5038	20,535
Opioid	5016	4742	5081	4493	19,332
Missing	53	55	25	29	162

TABLE 25 Opioid vs. non-opioid analgesic medications split by comparison groups

Analgesic	No ZA	ZA	No Sr-89	Sr-89
Number of patients				
Non-opioid	175	172	169	178
Opioid	112	113	123	102
Missing	2	1	2	1
Number of instances				
Non-opioid	10,391	10,144	10,309	10,225
Opioid	10,097	9235	9758	9574
Missing	78	84	108	54

Clinical progression-free survival

Statistical methods

Descriptive analysis of CPFS events is presented as percentages. Kaplan–Meier curves were created and used to calculate CPFS percentages at 6, 12, 18 and 24 months. Analysis of CPFS has been carried out using both an unadjusted approach and an adjusted approach. The first analysis of the primary outcome was an unadjusted stratified log-rank test comparing ZA with no ZA, stratified by Sr-89, and comparing Sr-89 with no Sr-89, stratified by ZA. Conclusions were based on a two-sided 5% significance level. No adjustments for multiple testing were made.

The second analysis of the primary end point used an adjusted Cox regression model, including both treatment comparisons and stratification factors (ECOG and randomising centre). The use of stratification factors within the design leads to correlation between the treatment groups. These correlations, when not adjusted for, can lead to upwards biased standard error rates for treatment effects, CIs which are too wide, type 1 error rates which are too low and a subsequent reduction in power.[49,50] Owing to these potential implications, our primary outcome conclusions have been based on the adjusted Cox regression analysis. The use of both log-rank and Cox regression models was pre-specified in the trial protocol.

Further analysis included all prognostic factors recorded at baseline that were either statistically (stratification factors: ECOG, centre) or clinically (age, histology, prior radiotherapy use, anti-androgen use, presence of measurable lesions on bone scan, baseline alkaline phosphatase levels and baseline PSA levels) important. No optimal model-building techniques were employed. All factors listed were adjusted for in the model.

Clinical progression-free survival results

Tables 26 and *27* show a breakdown of the first CPFS event split by randomisation arms and comparison groups.

Thirty per cent of patients did not experience a SRE or pain progression prior to death. An audit was conducted of patients in this study which checked to see whether or not SREs or pain progression had gone unreported. The audit concluded that this was not the case and confirmed that approximately 30% of patients died without experiencing a preceding event.

In total, 696 of the 757 patients (92%) randomised experienced clinical progression. The median follow-up time of the 61 surviving patients who had not yet progressed is 20.9 months (IQR 16.3–24.8 months).

TABLE 26 Breakdown of CPFS by type of first event

	Docetaxel (*N* = 173)		Docetaxel + ZA (*N* = 174)		Docetaxel + Sr-89 (*N* = 171)		Docetaxel + ZA + Sr-89 (*N* = 178)		Overall (*N* = 696)	
Type of first CPFS event	*n*	%	*n*	%	*n*	%	*n*	%	*n*	%
Death	45	26.0	61	35.1	42	24.6	61	34.3	209	30.0
SRE	34	19.7	27	15.5	39	22.8	29	16.3	129	18.5
Pain	73	42.2	71	40.8	59	34.5	61	34.3	264	37.9
Death SRE	0	0.0	1	0.6	0	0.0	0	0.0	1	0.1
SRE pain	21	12.1	14	8.0	31	18.1	27	15.2	93	13.4
Total	173	100.0	174	100.0	171	100.0	178	100.0	696	100.0

TABLE 27 Breakdown of CPFS by type of first event analysis arm

	No ZA (*N* = 344)		ZA (*N* = 352)		No Sr-89 (*N* = 347)		Sr-89 (*N* = 349)	
Type of first CPFS event	*n*	%	*n*	%	*n*	%	*n*	%
Death	87	25.3	122	34.7	106	30.5	103	29.5
SRE	73	21.2	56	15.9	61	17.6	68	19.5
Pain	132	38.4	132	37.5	144	41.5	120	34.4
Death SRE	0	0.0	1	0.3	1	0.3	0	0.0
SRE pain	52	15.1	41	11.6	35	10.1	58	16.6
Total	344	100.0	352	100.0	347	100.0	349	100.0

Zoledronic acid versus no zoledronic acid

In total, there were 696 events; 352 (51%) occurred in the ZA group and 344 (49%) in the no ZA group. A stratified log-rank test was performed comparing ZA and no ZA. No difference in CPFS between the two groups was observed ($\chi^2 = 0.10$; $p = 0.7553$). The median survival time in the ZA group was 9.43 months (95% CI 8.51 to 9.89 months), compared with 8.57 months (95% CI 7.36 to 9.33 months) in the no ZA group. A Cox proportional hazards model was used to estimate the HR (0.98, 95% CI 0.84 to 1.13; $p = 0.762$).

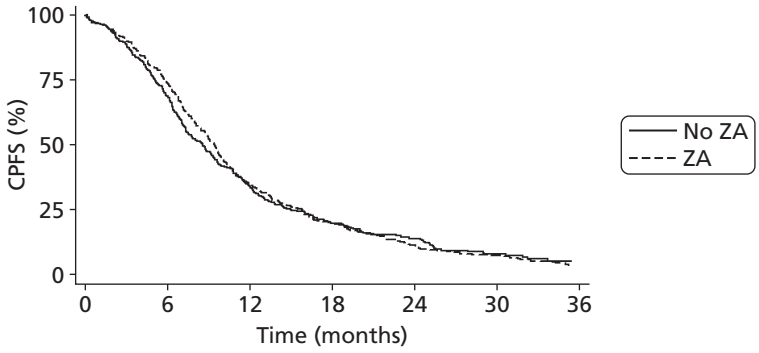
Table 28 shows the estimated clinical-related progression-free survival percentages at 6-monthly intervals, with 95% CIs.

It can be clearly seen that the estimated survival percentage is almost exactly the same at 12 and 18 months.

Figure 13 shows the Kaplan–Meier survival estimates split by comparison ZA. The Kaplan–Meier curve shows very clearly that there was virtually no difference between the ZA and no ZA groups.

TABLE 28 Estimated clinical-related progression-free survival percentages

Time point	% survival (95% CI), no ZA	% survival (95% CI), ZA
6 months	68 (64 to 73)	74 (69 to 78)
12 months	34 (29 to 39)	34 (30 to 39)
18 months	20 (16 to 24)	20 (16 to 24)
24 months	14 (10 to 18)	11 (8 to 15)



Number at risk No ZA	381	260	127	67	36	15	8
ZA	376	275	127	69	32	18	8

FIGURE 13 Kaplan–Meier survival estimates of CPFS by ZA comparison. Reproduced with permission from *JAMA Oncol*, 2016;**2**(4):493–9. Copyright © (2016) American Medical Association. All rights reserved.[51]

Strontium-89 versus no strontium-89

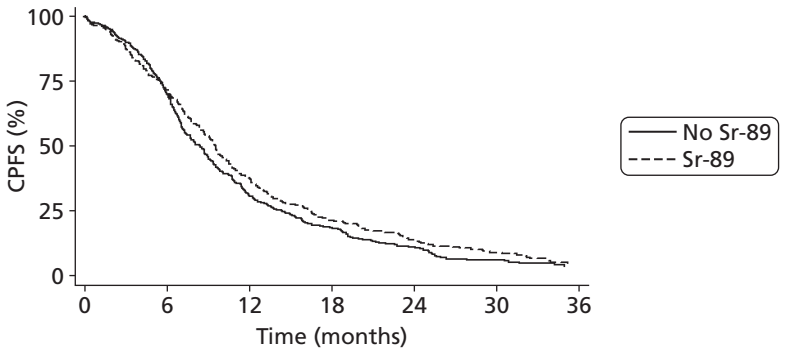
In total, there were 696 events: 349 (50%) in the Sr-89 group and 347 (50%) in the no Sr-89 group. A stratified log-rank test comparing Sr-89 and no Sr-89 revealed no difference in CPFS between the two groups ($\chi^2 = 2.38$; $p = 0.1230$). The median survival time in the Sr-89 arm was 9.56 months (95% CI 8.74 to 10.25 months), compared with 8.38 months (95% CI 7.36 to 9.07 months) in the no Sr-89 arm. A Cox proportional hazards model was used to estimate the HR (0.88, 95% CI 0.76 to 1.03; $p = 0.108$).

Table 29 shows the estimated CPFS survival percentages at 6-monthly intervals with 95% CIs.

Figure 14 shows the Kaplan–Meier survival estimates split by comparison of Sr-89 treatment. A small difference from approximately 6 months to 3 years is visible, although this is not statistically significant according to the log-rank test.

TABLE 29 Estimated clinical-related progression-free survival percentages for Sr-89

Time point	% survival (95% CI), no Sr-89	% survival (95% CI), Sr-89
6 months	71 (66 to 75)	71 (67 to 76)
12 months	31 (26 to 35)	38 (33 to 42)
18 months	18 (14 to 22)	21 (17 to 25)
24 months	11 (8 to 15)	14 (10 to 18)



Number at risk No Sr-89	379	266	114	59	27	13	7
Sr-89	378	269	140	77	41	20	9

FIGURE 14 Kaplan–Meier survival estimates of CPFS by Sr-89 comparison. Reproduced with permission from *JAMA Oncol*, 2016;**2**(4):493–9. Copyright © (2016) American Medical Association. All rights reserved.[51]

Interaction

The two-by-two factorial design assumed no interaction between Sr-89 and ZA. This assumption was investigated both graphically and by inclusion of interaction terms within a Cox model, which revealed no evidence of an interaction between the two treatments ($\chi^2 = 0.70$; $p = 0.4035$).

Secondary analysis adjusting for stratification factors

The secondary analyses of the primary outcome used a Cox multivariable proportional hazards model, including both treatment comparisons, ECOG performance status (fixed effect) and randomising centre (random effect).

Cox model

Table 30 shows the HRs, *p*-values and the 95% CIs for the HRs from the Cox model.

A Cox proportional hazards model looking at treatment effects while controlling for important covariates demonstrated a statistically significant effect of Sr-89, albeit with only a moderate HR (0.85, 95% CI 0.73 to 0.99; $p = 0.03$); however, there was no statistically significant effect of ZA (HR 0.98, 95% CI 0.84 to 1.14; $p = 0.80$).

Analysis adjusting for all potential prognostic factors

Table 31 shows the results of Cox proportional hazards model analysis adjusting for all statistically and clinically significant factors.

A Cox proportional hazards model looking at treatment effects while controlling for important covariates demonstrated a statistically significant effect of Sr-89 (HR 0.81, 95% CI 0.70 to 0.95; $p = 0.01$), but no statistically significant effect of ZA (HR 0.99, 95% CI 0.85 to 1.16; $p = 0.93$). Other factors shown to be associated with reduced risk of CPFS were good performance status, increased age, no previous radiotherapy, low PSA and low alkaline phosphatase levels. The proportionality assumption was assessed and found to be upheld.

TABLE 30 Cox proportional hazards model including stratification factors

			95% CI	
Variable	**HR**	***p*-value**	**Lower limit**	**Upper limit**
Sr-89 (ref.: no Sr-89)				
Sr-89	0.847	0.031	0.729	0.985
ZA (ref.: no ZA)				
ZA	0.982	0.808	0.845	1.141
ECOG (ref.: ECOG 0)				
ECOG 1	1.547	< 0.001	1.315	1.821
ECOG 2	2.136	< 0.001	1.603	2.847
Random effect of centre				
Centre	–	< 0.001	–	–

Ref., reference.

TABLE 31 Cox proportional hazards model including important covariates

Variable	HR	*p*-value	95% CI	
			Lower limit	Upper limit
Sr-89 (ref.: no Sr-89)				
Sr-89	0.814	0.010	0.696	0.952
ZA (ref.: no ZA)				
ZA	0.993	0.933	0.851	1.160
ECOG (ref.: ECOG 0)				
ECOG 1	1.605	< 0.001	1.350	1.909
ECOG 2	1.895	< 0.001	1.397	2.570
Age (years)				
1-year increase	0.977	< 0.001	0.965	0.988
Histology (ref.: adenocarcinoma)				
Elevated PSA	0.970	0.771	0.791	1.190
Prior radiotherapy (ref.: no)				
Yes	1.221	0.016	1.039	1.436
Anti-androgens (ref.: no)				
Yes	0.773	0.084	0.578	1.035
Measurable lesions on bone scan (ref.: no)				
Yes	1.181	0.058	0.994	1.403
Baseline alkaline phosphatase				
100-unit increase	1.025	< 0.001	1.016	1.033
Baseline PSA				
100-unit increase	1.016	0.019	1.003	1.030
Random effect of centre				
Centre	–	< 0.001	–	–

Ref., reference.

Skeletal-related events

Statistical methods

Descriptive analysis of types of SREs is presented as percentages, progression between different types of SREs and the time between them diagrammatically and Kaplan–Meier curves were used to present SREFIs.

The primary analysis was a stratified log-rank comparing ZA with no ZA, stratified by Sr-89 and Sr-89, with no Sr-89 stratified by ZA. Conclusions were based on a two-sided 5% significance level. No adjustments for multiple testing were made.

Sensitivity analysis

Owing to the high proportion of patients who were randomised to Sr-89 but unable to receive it, a per-protocol analysis was conducted on a per-protocol population. The per-protocol population is defined as all eligible patients who received six cycles of docetaxel and did not experience pain progression or a SRE prior to 21 days following the sixth administration of docetaxel and therefore would have been able to

receive Sr-89. The definition of SREFIs will remain the same as detailed above, as will the Kaplan–Meier method and stratified log-rank test used.

Multiple failure model

The previously defined log-rank time-to-event analysis took into account only the time-to-first SRE, although patients were at risk of experiencing multiple SREs throughout the course of the trial. It was, therefore, conceivable that a medication may have had little or no effect on the time-to-first event but could prevent patients experiencing multiple events. To take account of this, a multiple failure model was employed.

There were three factors to consider when deciding on the appropriate multiple failure methodology. First, a patient could experience multiple SREs on the same day. Second, SREs were ordered in the sense that a second event could not occur without a first event having been experienced. Finally, for subsequent SREs the time-to-event needed to be measured from the date of the previous SRE and not from randomisation. For example, once a patient had experienced a first SRE, his risk of having a subsequent event changed, as it was considered feasible to assume that having the first SRE would change the underlying hazard in this disease setting. To take account of all of these factors, a multiple failure model was used, specifically the conditional risk set model proposed by Prentice *et al.*[52] Once the model was set up to account for the multiple events, Kaplan–Meier stratified log-rank methods were employed as previously described.

Descriptive statistics of skeletal-related events

Tables 32 and *33* show the breakdown of the types of SREs that occurred, split by randomisation arm and comparison groups. The occurrence of more serious SREs, that is fracture, SCC and surgery, was consistently higher in the no ZA group than the ZA group, although the overall distribution of SREs within groups was similar.

Table 34 shows number of patients experiencing SREs by comparison group. The numbers of patients experiencing multiple SREs is lower in the ZA group.

Diagrams showing the order in which different types of SREs occurred and the time between these events can be found in *Appendix 5*, *Figures 55–74*. These show that the overall time to the first SRE is longer in the no ZA group than in the ZA group. The difference is approximately 1.5 months if radiation, fracture or change of therapy was the first SRE and approximately 5.5 months if the first SRE was SCC. In both ZA and no ZA groups, radiation was by far the most common first SRE, with change in therapy being the second most common, followed by SCC. The proportion of first SREs which were SCCs in the no ZA arm was almost double that in the ZA arm. The ZA group also saw fewer instances of subsequent SREs being for surgery or SCC.

In terms of the Sr-89 comparison, there were fewer differences, with both the no Sr-89 and the Sr-89 groups having similar distributions of the type of events and times to the first events. The only exception was when SCC was the first event, in which case the time to first event was 2.5 months longer for those receiving Sr-89 than for those who were not.

TABLE 32 Type of SRE by randomisation arm

	Docetaxel		Docetaxel + ZA		Docetaxel + Sr-89		Docetaxel + ZA + Sr-89		Overall	
Type of SRE	*n*	%	*n*	%	*n*	%	*n*	%	*n*	%
Fractures	12	3.8	5	2.3	18	6.3	7	3.4	42	4.1
SCC	31	9.8	13	6	30	10.4	21	10.2	95	9.2
Surgery	7	2.2	4	1.8	14	4.9	2	1	27	2.6
Radiation	221	69.7	158	72.5	171	59.4	140	68	690	67.1
Change of therapy	46	14.5	38	17.4	53	18.4	36	17.5	173	16.8
Hypercalcaemia	0	0	0	0	2	0.7	0	0	2	0.2
Total	317	100.0	218	100.0	288	100.0	206	100.0	1029	100.0

TABLE 33 Type of SRE by ZA and Sr-89 comparison group

	No ZA		ZA		No Sr-89		Sr-89	
Type of SRE	*n*	%	*n*	%	*n*	%	*n*	%
Fractures	30	5	12	2.8	17	3.2	25	5.1
SCC	61	10.1	34	8	44	8.2	51	10.3
Surgery	21	3.5	6	1.4	11	2.1	16	3.2
Radiation	392	64.8	298	70.3	379	70.8	311	63
Change of therapy	99	16.4	74	17.5	84	15.7	89	18
Hypercalcaemia	2	0.3	0	0	0	0	2	0.4
Total	605	100.0	424	100.0	535	100.0	494	100.0

TABLE 34 Number of patients experiencing multiple SREs by comparison group

	ZA comparison		Sr-89 comparison	
Number of SREs	No ZA	ZA	No Sr-89	Sr-89
	n *(%)*	**n *(%)***	**n *(%)***	**n *(%)***
None	147 (39)	173 (46)	157 (41)	163 (43)
1	80 (21)	100 (27)	90 (24)	90 (24)
2	57 (15)	45 (12)	52 (14)	50 (13)
3	40 (10)	29 (8)	35 (9)	34 (9)
4	21 (5)	13 (3)	15 (4)	19 (5)
5	22 (6)	10 (2)	17 (5)	15 (4)
≥ 6	14 (4)	6 (2)	13 (3)	7 (2)
Total number of patients	381 (100)	376 (100)	379 (100)	378 (100)
Number reporting at least one SRE	234 (61)	203 (54)	222 (59)	215 (57)

Skeletal-related event-free interval

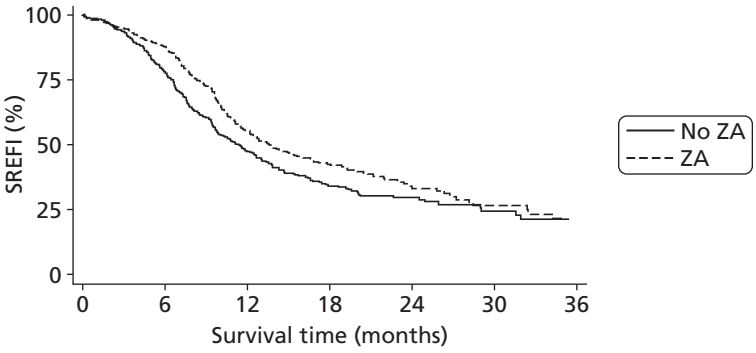
Zoledronic acid versus no zoledronic acid

In total, there were 437 events: 234 (54%) in the no ZA group and 203 (46%) in the ZA group. A stratified log-rank test was performed comparing ZA with no ZA. A statistically significant difference in SREFIs between the two groups was observed ($\chi^2 = 6.49$, $p = 0.011$). The median survival time in the ZA group was 13.60 months (95% CI 11.76 to 16.62 months), compared with 11.17 months (95% CI 9.76 to 13.01 months) in the no ZA group.

A Cox proportional hazards model was used to estimate the HR (0.78, 95% CI 0.65 to 0.95; $p = 0.011$). *Figure 15* shows the Kaplan–Meier survival estimates split by comparison group: ZA.

Strontium-89 versus no strontium-89

In total, there were 437 events: 222 (51%) in the no Sr-89 group and 215 (49%) in the Sr-89 group. A stratified log-rank test was performed comparing Sr-89 with no Sr-89. No difference in SREFI between the two groups was observed ($\chi^2 = 1.89$; $p = 0.169$). The median survival time in the Sr-89 group was 13.04 months (95% CI 11.14 to 14.69 months), compared with 11.70 months (95% CI 10.58 to 13.60 months) in the no Sr-89 group.



Number at risk No ZA	381	271	142	76	42	19	9
ZA	376	299	158	84	40	21	10

FIGURE 15 Kaplan–Meier survival estimates of SREFIs by comparison group: ZA. Reproduced with permission from *JAMA Oncol*, 2016;**2**(4):493–9. Copyright © (2016) American Medical Association. All rights reserved.[51]

A Cox proportional hazards model was used to estimate the hazard ratio (HR 0.88, 95% CI 0.73 to 1.06; $p = 0.170$). *Figure 16* shows the Kaplan–Meier survival estimates split by Sr-89 comparison.

Landmark analysis for strontium-89

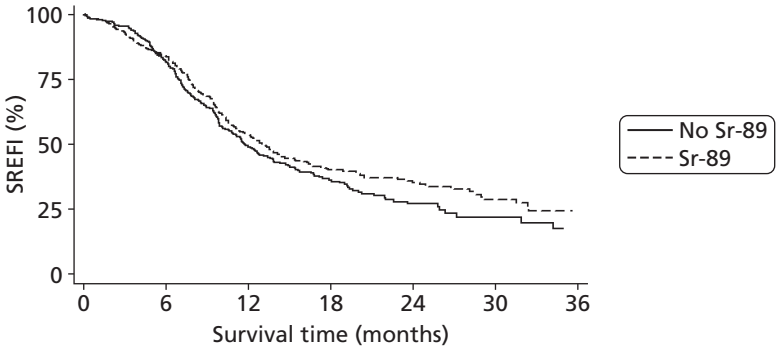
In total, 531 (70%) patients received six cycles of docetaxel and were therefore eligible to receive Sr-89.

Of a total of 321 events, 162 (50%) occurred in the no Sr-89 group and 159 (50%) in the Sr-89 group. A stratified log-rank test was performed comparing Sr-89 with no Sr-89. No difference in SREFI between the two groups was observed ($\chi^2 = 2.27$; $p = 0.132$). The median survival time in the Sr-89 arm was 14.16 months (95% CI 12.52 to 17.74 months), compared with 12.75 months (95% CI 11.43 to 15.38 months) in the no Sr-89 arm.

A Cox proportional hazards model was used to estimate the HR (HR 0.85, 95% CI 0.68 to 1.05; $p = 0.170$). *Figure 17* shows the Kaplan–Meier survival estimates split by comparison Sr-89.

Multiple failure model

As seen in the *Descriptive statistics of skeletal-related events*, patients experience multiple SREs. The previous time-to-event analysis looks at only time-to-first event, not taking multiple SREs into account. The following section takes the multiple events into account, as detailed in this section's statistical methods.



Number at risk No Sr-89	379	283	140	66	30	14	7
Sr-89	378	287	160	94	52	26	12

FIGURE 16 Kaplan–Meier survival estimates of SREFI by comparison group: Sr-89. Reproduced with permission from *JAMA Oncol*, 2016;**2**(4):493–9. Copyright © (2016) American Medical Association. All rights reserved.[51]

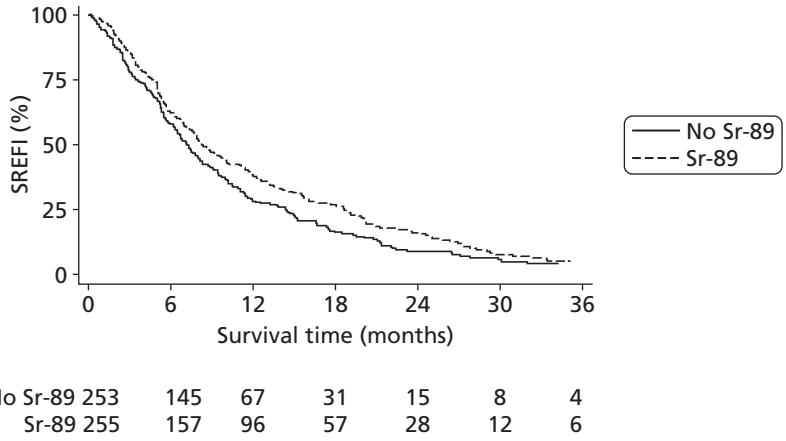


FIGURE 17 Kaplan–Meier survival estimates of SREFIs by Sr-89.

There were 33 instances where patients experienced multiple SREs on the same day; for the purposes of this analysis such events were counted as a single event.

Zoledronic acid versus no zoledronic acid

In total, there were 996 events: 584 (59%) in the no ZA group and 412 (41%) in the ZA group. A stratified log-rank test comparing ZA with no ZA demonstrated a statistically significant difference in SREFIs between the two groups ($\chi^2 = 31.39$; $p < 0.001$). The median survival time in the ZA group was 11.5 months (95% CI 10.61 to 12.65 months), compared with 8.87 months (95% CI 7.85 to 9.66 months) in the no ZA group.

A Cox proportional hazards model was used to estimate the HR (HR 0.70, 95% CI 0.62 to 0.79; $p < 0.001$). *Figure 18* shows the Kaplan–Meier survival estimates split by comparison ZA.

Strontium-89 versus no strontium-89

In total, there were 996 events: 518 (52%) in the no Sr-89 group and 478 (48%) in the Sr-89 group. A stratified log-rank test performed to compare Sr-89 with no Sr-89 observed no difference in SREFI between the two groups ($\chi^2 = 3.11$; $p = 0.078$). The median survival time in the Sr-89 group was 10.41 months (95% CI 9.69 to 11.14 months), compared with 9.86 months (95% CI 9.13 to 10.81 months) in the no Sr-89 group.

A Cox proportional hazards model was used to estimate the HR (HR 0.89, 95% CI 0.79 to 1.01; $p = 0.078$). *Figure 19* shows the Kaplan–Meier survival estimates split by Sr-89 comparison.

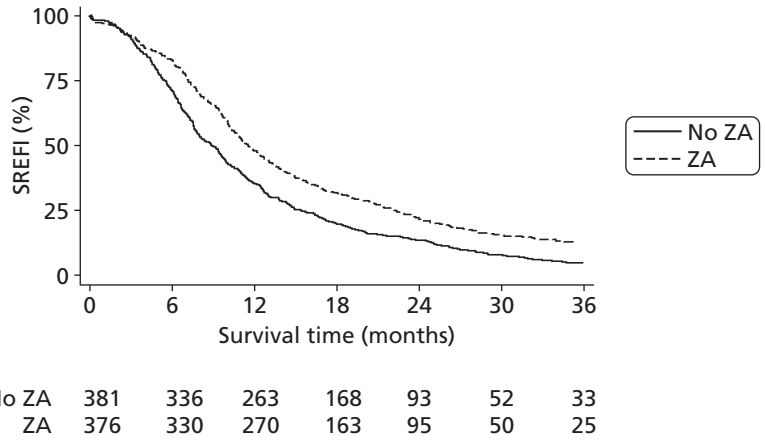
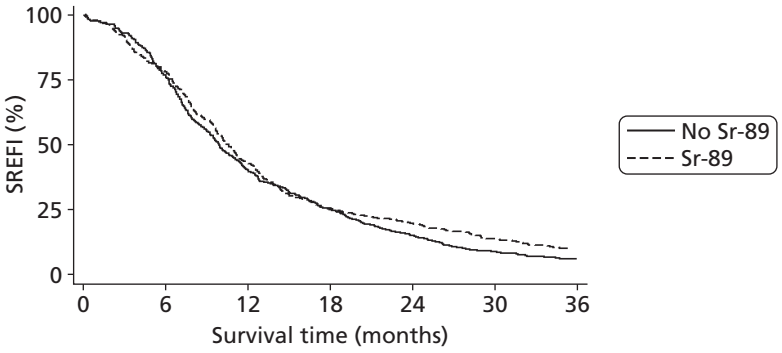


FIGURE 18 Kaplan–Meier survival estimates for SREFI multiple failure model by ZA comparison.



Number at risk No Sr-89	379	333	265	154	89	48	26
Sr-89	378	333	268	177	99	54	32

FIGURE 19 Kaplan–Meier survival estimates for SREFI multiple failure model by Sr-89 comparison.

Pain progression-free interval

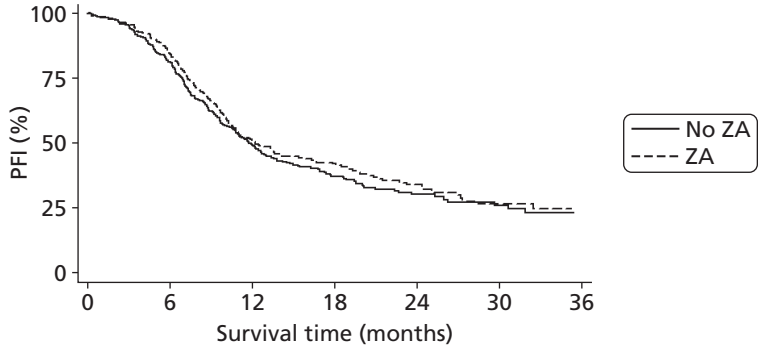
Statistical methods

The primary analysis was a stratified log-rank test comparing ZA with no ZA, stratified by Sr-89, and Sr-89 with no Sr-89, stratified by ZA. Conclusions were based on a two-sided 5% significance level. No adjustments for multiple testing were made.

Zoledronic acid versus no zoledronic acid

In total, there were 432 events: 225 (52%) in the no ZA group and 207 (48%) in the ZA group. A stratified log-rank test was performed comparing ZA with no ZA. No difference in PPFI between the two groups was observed ($\chi^2 = 1.02$; $p = 0.3127$). The median progression-free survival time in the ZA group was 12.19 months (95% CI 10.78 to 15.38 months), compared with 11.76 months (95% CI 10.55 to 13.37 months) in the no ZA group.

A Cox proportional hazards model was used to estimate the HR (HR 0.91, 95% CI 0.75 to 1.10; $p = 0.313$). *Figure 20* shows the Kaplan–Meier survival estimates split by ZA comparison.



Number at risk No ZA	381	281	149	81	43	20	11
ZA	376	285	143	81	39	20	10

FIGURE 20 Kaplan–Meier survival estimates for PPFI by ZA.

Strontium-89 versus no strontium-89

In total, there were 432 events: 215 (50%) in the no Sr-89 group and 217 (50%) in the Sr-89 group. A stratified log-rank test was performed comparing Sr-89 with no Sr-89. No difference in PPFI between the two groups was observed ($\chi^2 = 0.40$; $p = 0.3991$). The median PPFI time in the Sr-89 group was 12.22 months (95% CI 10.94 to 14.09 months), compared with 11.76 months (95% CI 10.32 to 13.54 months) in the no Sr-89 group.

A Cox proportional hazards model was used to estimate the HR (HR 0.92, 95% CI 0.76 to 1.11; $p = 0.387$). *Figure 21* shows the Kaplan–Meier survival estimates split by Sr-89 comparison.

Overall survival

Statistical methods

The primary analysis was a stratified log-rank comparing ZA with no ZA, stratified by Sr-89, and Sr-89 versus no Sr-89, stratified by ZA. Conclusions were based on a two-sided 5% significance level. No adjustments for multiple testing were made.

Descriptive statistics of deaths

In total, 618 patients died. *Tables 35* and *36* list the reported causes of death split by randomisation arm and comparison groups.

Overall survival: zoledronic acid versus no zoledronic acid

In total, there were 618 events: 309 (50%) occurred in each group. A stratified log-rank test performed to compare ZA with no ZA demonstrated no difference in OS between the two groups ($\chi^2 = 0.01$; $p = 0.909$). The median survival time in the ZA group was 16.99 months (95% CI 16.07 to 19.23 months), compared with 17.61 months (95% CI 16.10 to 18.96 months) in the no ZA group.

A Cox proportional hazards model was used to estimate the HR (HR 0.99, 95% CI 0.84 to 1.16; $p = 0.870$). *Figure 22* shows the Kaplan–Meier survival estimates split by ZA comparison.

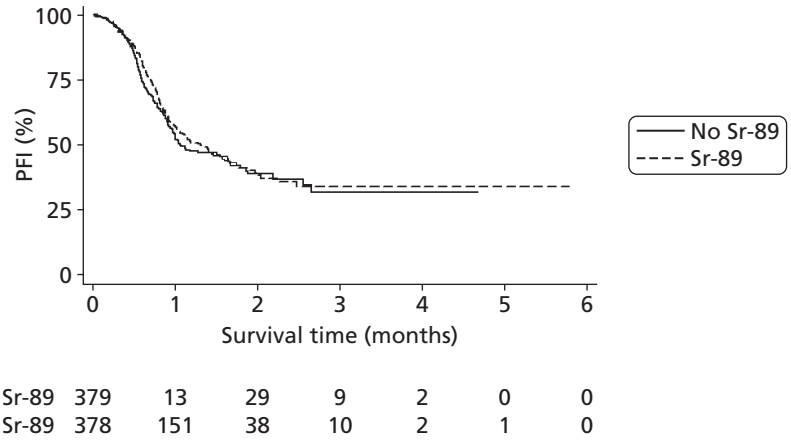


FIGURE 21 Kaplan–Meier survival estimates for PPFI by Sr-89.

TABLE 35 Cause of death by randomisation arm

	Docetaxel (*N* = 154)		Docetaxel + ZA (*N* = 156)		Docetaxel + Sr-89 (*N* = 155)		Docetaxel + ZA + Sr-89 (*N* = 153)		Overall (*N* = 618)	
Cause of death	***n***	**%**	***n***	**%**	***n***	**%**	***n***	**%**	***n***	**%**
Disease related	122	91.0	118	84.9	128	92.1	122	89.1	490	89.3
Trial treatment related	0	0.0	4	2.9	0	0.0	0	0.0	4	0.7
Disease and trial treatment related	0	0.0	1	0.7	0	0.0	1	0.7	2	0.4
Other cancer	0	0.0	0	0.0	0	0.0	1	0.7	1	0.2
Other non-cancer	11	8.2	15	10.8	10	7.2	12	8.8	48	8.7
Non-trial treatment related	1	0.7	1	0.7	1	0.7	1	0.7	4	0.7
Unknown	20	–	17	–	16	–	16	–	69	–
Total	134	100.0	139	100.0	139	100.0	137	100.0	549	100.0

TABLE 36 Cause of death by comparison group

	No ZA (*N* = 309)		ZA (*N* = 309)		No Sr-89 (*N* = 310)		Sr-89 (*N* = 308)	
Cause of death	***n***	**%**	***n***	**%**	***n***	**%**	***n***	**%**
Disease related	250	91.6	240	87	240	87.9	250	90.6
Trial treatment related	0	0	4	1.4	4	1.5	0	0
Disease and trial treatment related	0	0	2	0.7	1	0.4	1	0.4
Other cancer	0	0	1	0.4	0	0	1	0.4
Other non-cancer	21	7.7	27	9.8	26	9.5	22	8
Non-trial treatment related	2	0.7	2	0.7	2	0.7	2	0.7
Unknown	36	–	33	–	37	–	32	–
Total	273	100	276	100	273	100	276	100

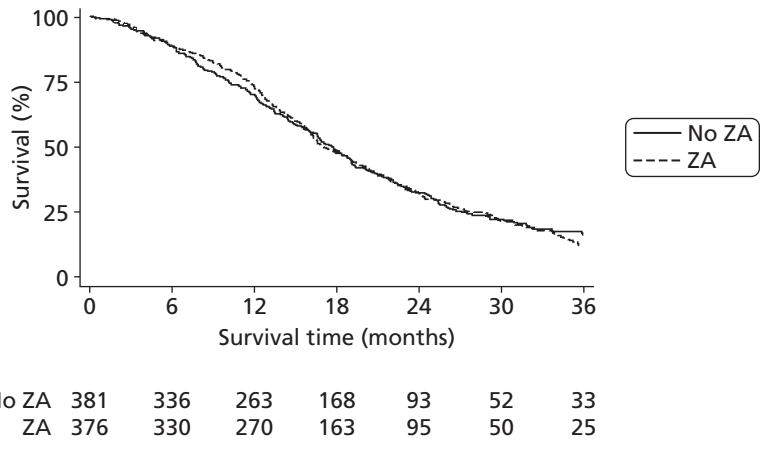


FIGURE 22 Kaplan–Meier estimates of OS by ZA.

Strontium-89 versus no strontium-89

In total, there were 618 events: 310 (50%) in the no Sr-89 group and 308 in the Sr-89 (50%) group. A stratified log-rank test performed to compare Sr-89 with no Sr-89 demonstrated no difference in OS between the two groups ($\chi^2 = 0.93$; $p = 0.3359$). The median survival time in the Sr-89 group was 18.17 months (95% CI 16.66 to 19.12 months), compared with 16.59 months (95% CI 15.61 to 18.27 months) in the no Sr-89 group.

A Cox proportional hazards model was used to estimate the HR (HR 0.92, 95% CI 0.79 to 1.08; $p = 0.323$). *Figure 23* shows the Kaplan–Meier survival estimates split by Sr-89 comparison.

Quality of life

Statistical methods

The EQ-5D, VAS and FACT-P are presented descriptively using means, standard deviations and ranges for the comparison groups. In addition, all are presented graphically to look for patterns emerging over time. It was also considered that SREs may have an effect on patients' QoL; therefore, patients were categorised as having no SREs, mild SREs or severe SREs, and these were investigated descriptively. In all cases, missing data for single items on questionnaires were dealt with in accordance with the manuals provided.

Quality-adjusted life-year analysis using subject-based approaches

Quality-adjusted life-years were utilised in two ways: subject- and group-based approaches. The first approach to QALY analysis was area-under-the-curve analysis, which was employed to investigate whether or not there were any differences between the comparison groups. As is usual with QoL data, there are more missing data towards the end of life. Therefore, three different methods were used to calculate QALYs to assess the impact of different assumptions, which can be seen in *Figure 24*. All deceased patients were treated in the same way. As only minimal changes in EQ-5D scores over time had been observed, the last QoL score was carried forward to the date the patient was last known to be alive and then a diagonal line was imputed from that date to date of death (see *Figure 24a*). For those patients still alive at the time of analysis, three separate approaches were taken. The first (see *Figure 24b*) made no imputation and the curve was dropped straight down at the date of the last EQ-5D score. This is a conservative approach, as it makes the inference that the patient died on the day his last EQ-5D

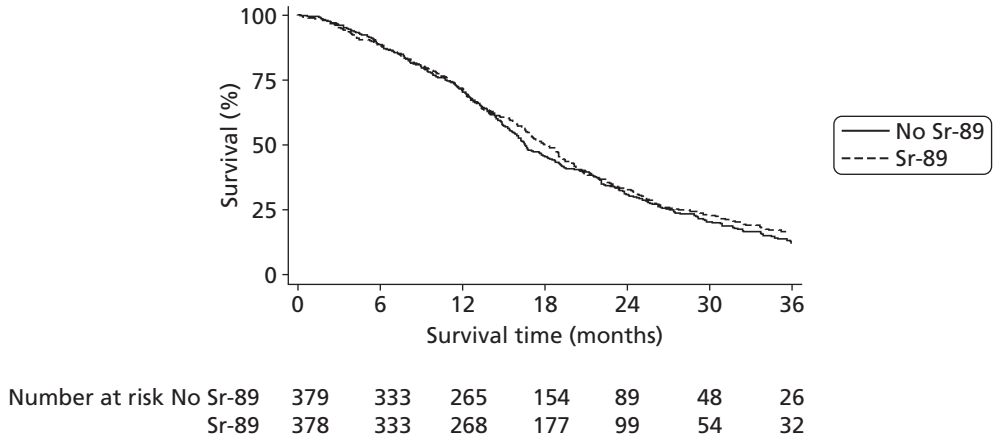


FIGURE 23 Kaplan–Meier estimates of OS by Sr-89.

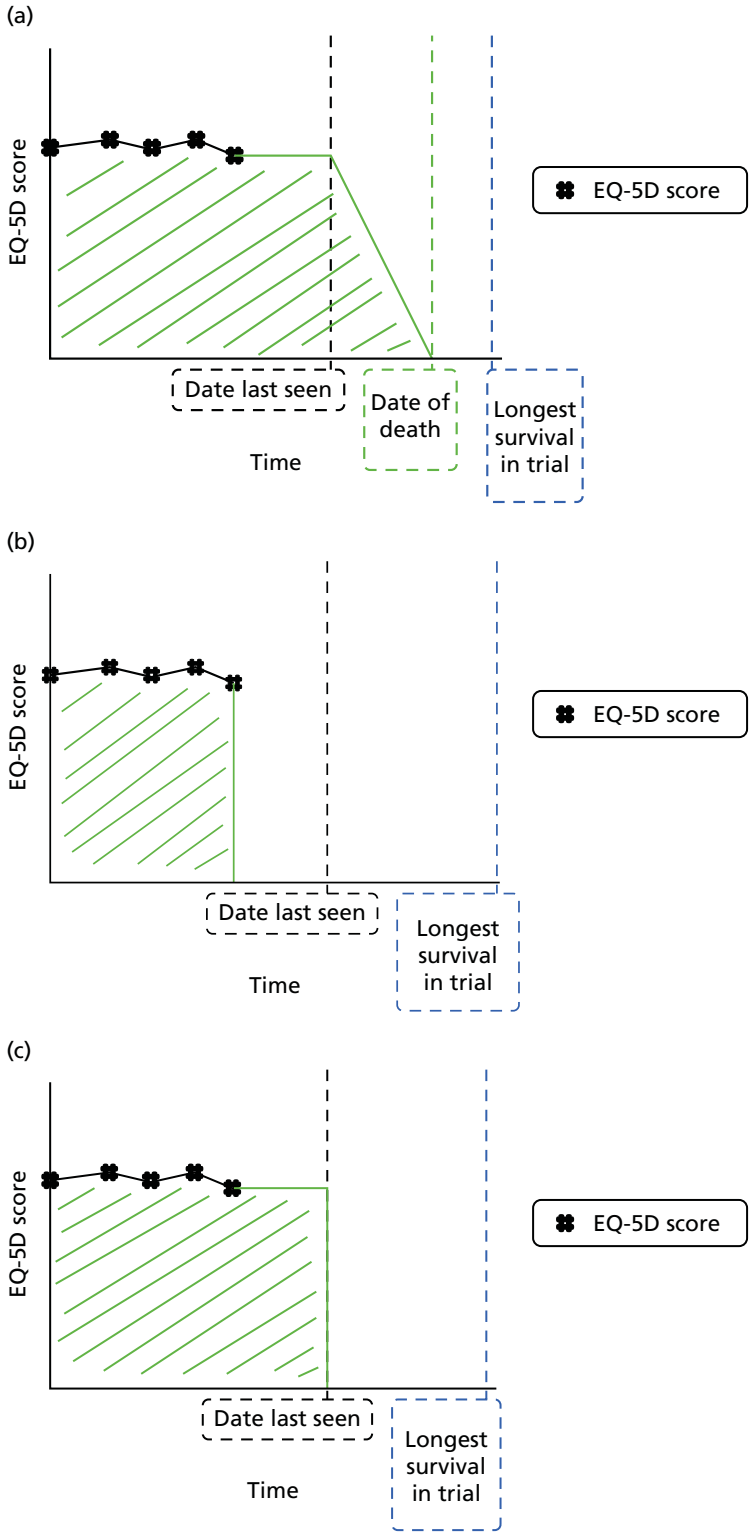


FIGURE 24 Method of calculating QALYs. (a) Deceased patients; (b) alive patients: conservative approach; (c) alive patients: standard approach; and (d) alive patients: optimistic approach. (*continued*)

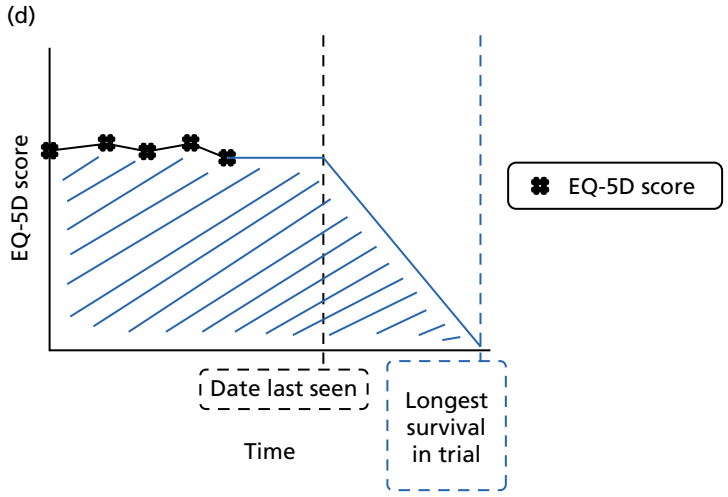


FIGURE 24 Method of calculating QALYs. (a) Deceased patients; (b) alive patients: conservative approach; (c) alive patients: standard approach; and (d) alive patients: optimistic approach.

questionnaire was collected. The other extreme of this was termed the optimistic approach (see *Figure 24d*); this approach carried the last EQ-5D score forward to the date last seen and then assumed that the patient survived for the same amount of time as the longest-surviving patient in the study and a diagonal line was imputed to that point. The third approach (see *Figure 24c*) is a middle ground between the conservative and optimistic approaches. The EQ-5D score is carried forward to the date last seen and drops to zero at that point, therefore imputing EQ-5D scores up to the date that the patient was known to be alive but not beyond this point.

Quality-adjusted life-year analysis using group-based approaches

The second approach to QALY analysis was a pre-specified group-based quality-adjusted survival analysis conducted to assess the balance between QoL and survival. This approach takes account of dropout due to death and censoring. As the median overall survival in the trial was 1.4 years, 2 years was deemed the appropriate cut-off point for the quality-adjusted survival. The integrated quality survival product is the product of the survival[53] and EQ-5D QoL measures over the 2-year time period of interest. It is calculated using the following equation:

$$QAS(24) = \int_0^{24} Q(t)S(t)dt, \quad (1)$$

where $S(t)$ is the proportion of patients who survive to time t and $Q(t)$ is the mean EQ-5D QoL associated with those survivors. This methodology of integrating QoL and survival was carried out at a group level for both the ZA and Sr-89 comparisons. The area under the curve at 2 years gave the mean QALY for each group. Standard errors were calculated and 95% CIs constructed using bootstrapping techniques with 1000 replications.

Results

In total, 6100 QoL booklets were returned: 5802 (95%) had complete EQ-5D data, 5806 (95%) had complete EQ-5D VAS data and 5573 (91%) had complete FACT-P data.

The 6100 forms were completed by 707 patients, leaving 50 patients for whom no QoL data were available. These patients are therefore excluded from this section of the report.

Patients returned, on average, six questionnaires: 40 patients returned only one form and one patient returned 22 forms.

Of the 707 patients, 572 had died at the time of analysis and 135 remained alive and on follow-up. The median time from completing the last QoL form to death was 193 days (IQR 86–381 days), meaning that, on average, two questionnaires are missing at the end of a patient's life. For those patients alive, the median time from last QoL form to date last seen was 231 days (IQR 59–434 days). Again, there were, on average, two missing questionnaires. *Figure 25* shows the points at which each questionnaire was returned.

Six distinct lines can be seen at the start of the graph; these relate to the first six cycles of treatment. Subsequently, among those patients receiving Sr-89, there would be a longer gap between cycles 6 and 7. At this point, a large number of patients also started to progress and, thus, were withdrawn from treatment. As a result, their schedule of completion of QoL questionnaires changed, which explains why there was no discernible pattern after the first six chemotherapy cycles.

Health state thermometer

As mentioned previously, the EQ-5D VAS is a self-completed measure resembling a thermometer ranging from 0 to 100, on which patients mark how well they feel on any specific day. *Table 37* shows the average EQ-5D VAS scores for each of the comparison groups throughout the trial.

There is no discernible difference in health state overall. *Figure 26* shows the health state by ZA comparison over time and the number of deaths over time; it also shows this split by SRE severity.

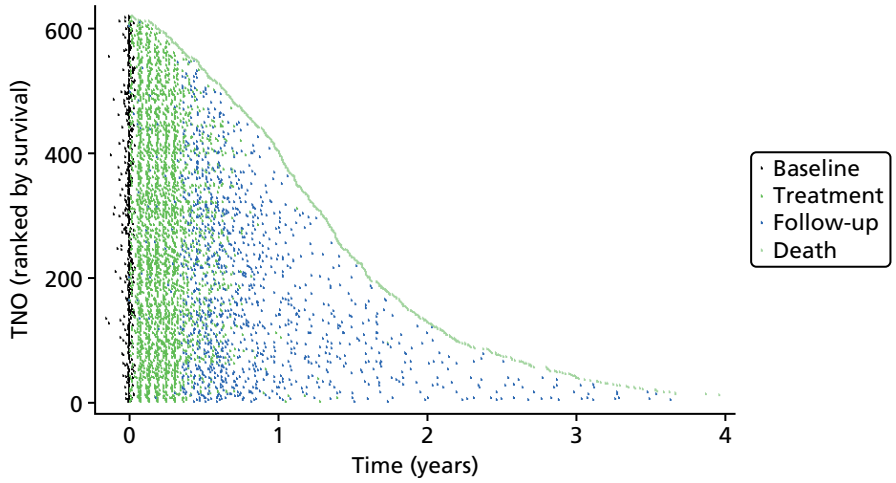


FIGURE 25 Quality-of-life questionnaire timings. TNO, trial number.

TABLE 37 Visual analogue scale split by ZA and Sr-89

Health state (score range: 0–100)	No ZA (*N* = 2905)	ZA (*N* = 2996)	No Sr-89 (*N* = 2920)	Sr-89 (*N* = 2981)
n	2905	2996	2920	2981
Mean (SD)	70.4 (19.5)	72.4 (17.6)	70.9 (18.4)	71.9 (18.7)
Range	0.0–100.0	0.0–100.0	0.0–100.0	0.0–100.0

SD, standard deviation.
N = number of QoL questionnaires returned.

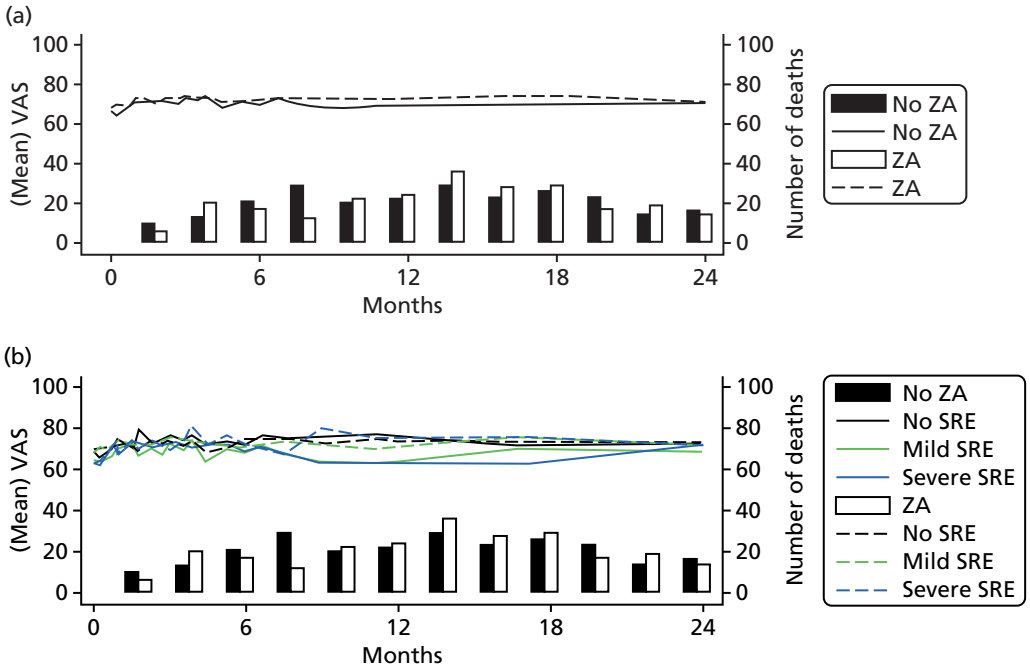


FIGURE 26 Visual analogue scale scores over time (lines) and number of deaths (boxes) by ZA comparison. (a) VAS score by ZA; and (b) VAS score by worst SRE and ZA.

Once the treatment period is complete, at about 6 months, the QoL of patients not receiving ZA seems to be consistently lower, particularly among those experiencing severe SREs, as would be expected.

Figure 27 below shows the health state by Sr-89 comparison over time and the number of deaths over time; it also shows this split by SRE severity.

Again, the QoL of those receiving Sr-89 appears to be consistently lower following the completion of treatment.

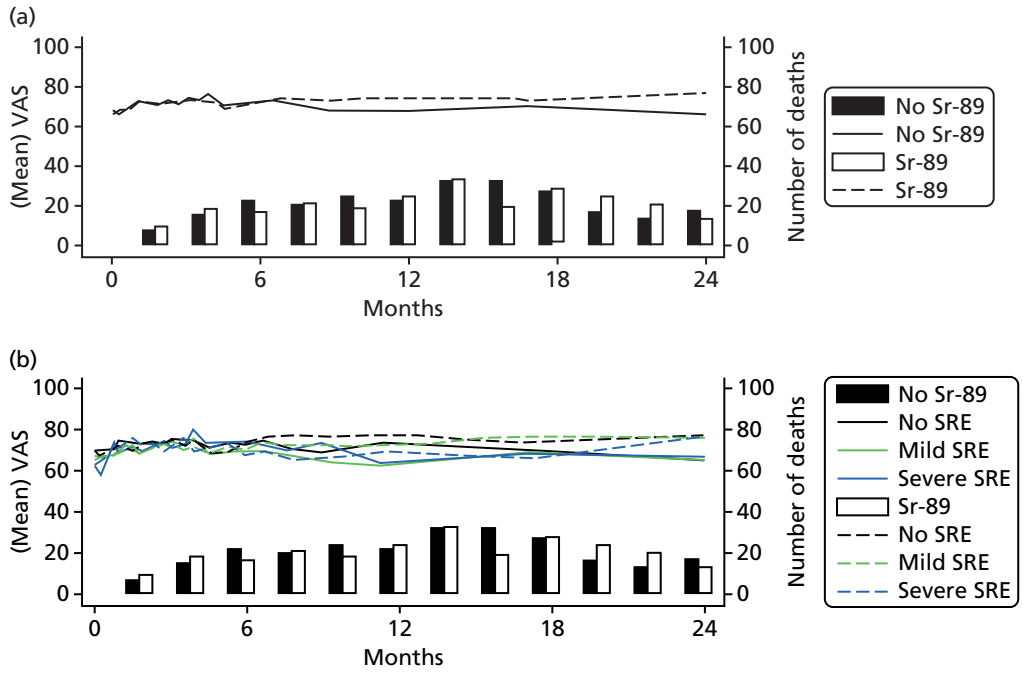


FIGURE 27 Visual analogue scale scores over time (lines) and number of deaths (boxes) by Sr-89 comparison. (a) VAS score by Sr-89; and (b) VAS score by worst SRE and Sr-89.

Functional Assessment of Cancer Therapy – Prostate

Table 38 shows the average score over the whole trial for each of the FACT-P subscales split by comparison groups.

As with health state scales, there are very few differences across the comparison groups overall. *Figure 28* shows a series of six graphs of the FACT-P subscale score over time split by ZA groups. *Figure 28f* also includes a bar chart of the numbers of deaths over time.

Each of the curves appears to show an increase in QoL within the first 2 months. It is most pronounced in the prostate cancer subscale and perhaps shows the positive effect of treatment in this patient population. The scales level off relatively quickly and remain constant and there is no visible decline in QoL; this is almost certainly at least in part due to missing data at the end of patients lives. The ZA line is very slightly higher in all of the graphs, and this is particularly apparent on the FACT-P graph, which is a summation of all of the subscales combined. *Figure 29* shows the same series of graphs for Sr-89.

TABLE 38 Average scores for FACT-P subscales by comparison groups

FACT-P	No ZA (*N* = 3005)	ZA (*N* = 3095)	No Sr-89 (*N* = 3022)	Sr-89 (*N* = 3078)
Physical well-being (score range: 0–28)				
n	2901	2993	2913	2981
Mean (SD)	21.7 (5.0)	22.1 (4.7)	21.7 (5.0)	22.1 (4.8)
Range	0.0–28.0	0.0–28.0	0.0–28.0	0.0–28.0
Social well-being (score range: 0–28)				
n	2914	3000	2921	2993
Mean (SD)	22.7 (4.5)	23.2 (4.3)	23.1 (4.5)	22.8 (4.2)
Range	0.0–28.0	0.0–28.0	0.0–28.0	0.0–28.0
Emotional well-being (score range: 0–24)				
n	2866	2970	2885	2951
Mean (SD)	18.9 (4.4)	19.3 (4.0)	18.9 (4.4)	19.2 (4.0)
Range	0.0–24.0	2.0–24.0	0.0–24.0	0.0–24.0
Functional well-being (score range: 0–28)				
n	2897	3004	2923	2978
Mean (SD)	18.4 (6.5)	18.9 (6.2)	18.5 (6.4)	18.8 (6.3)
Range	0.0–28.0	0.0–28.0	0.0–28.0	0.0–28.0
Prostate cancer (score range: 0–48)				
n	2901	3012	2916	2997
Mean (SD)	32.9 (7.7)	33.2 (7.4)	32.9 (7.5)	33.2 (7.6)
Range	3.0–48.0	6.5–48.0	3.0–48.0	3.0–48.0
FACT-P (score range: 0–156)				
n	2729	2844	2746	2827
Mean (SD)	114.6 (22.2)	116.9 (20.8)	115.2 (21.8)	116.3 (21.2)
Range	29.0–156.0	44.0–156.0	44.0–156.0	29.0–156.0

SD, standard deviation.
N = number of QoL forms.

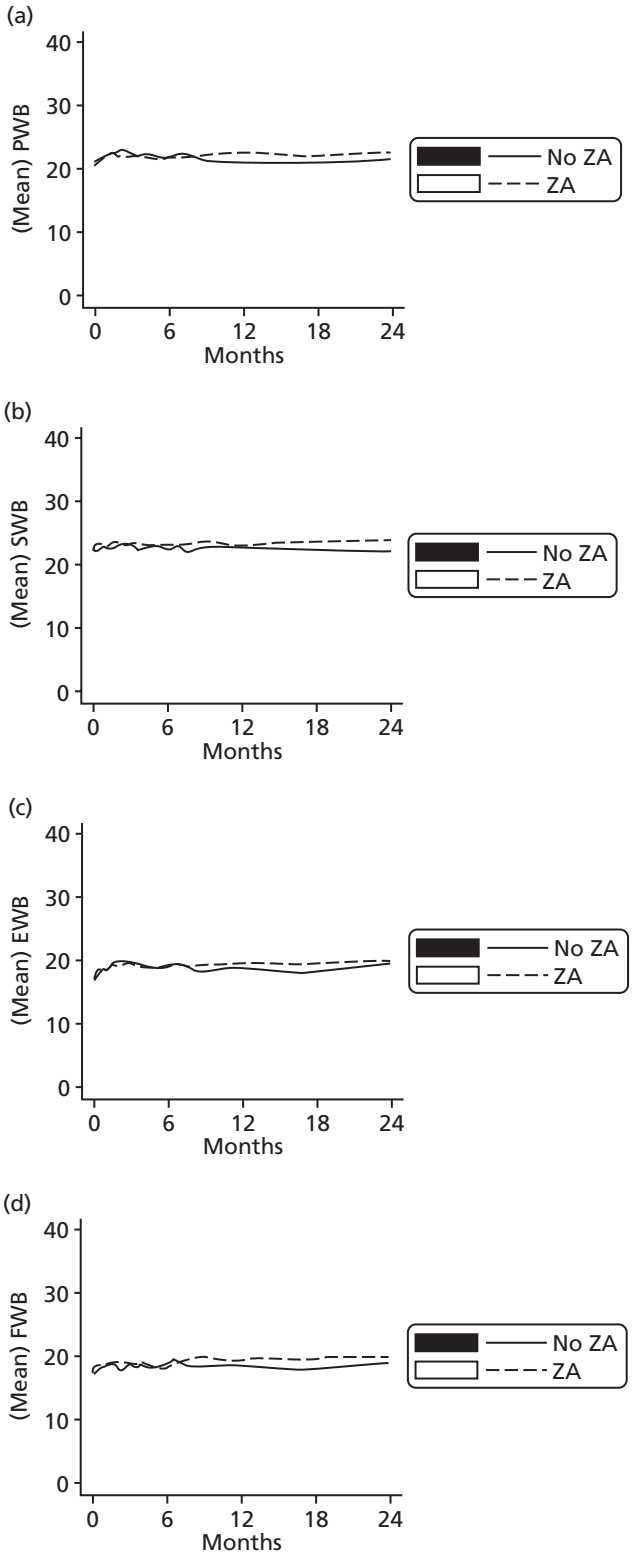


FIGURE 28 Functional Assessment of Cancer Therapy – Prostate subscales over time by ZA. (a) Physical well-being; (b) social well-being; (c) emotional well-being; (d) functional well-being; (e) prostate cancer; and (f) FACT-P. (*continued*)

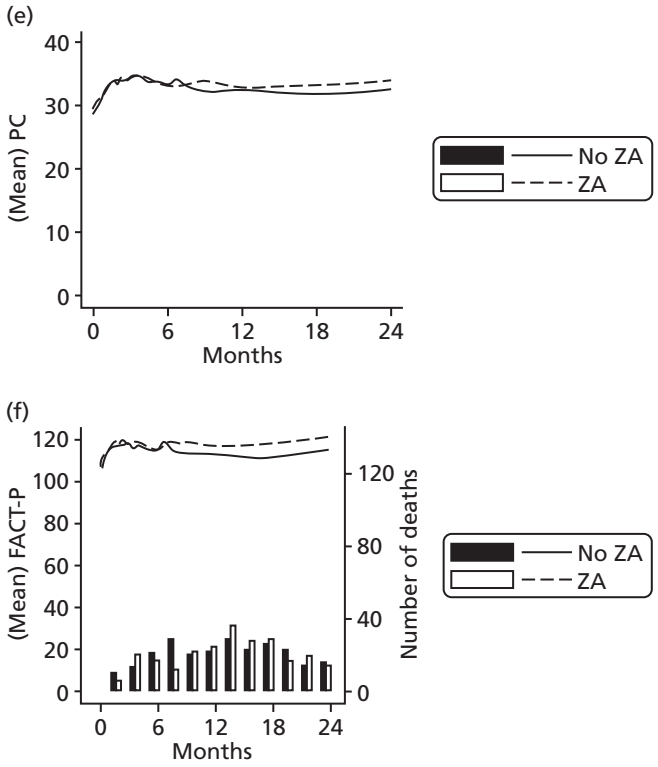


FIGURE 28 Functional Assessment of Cancer Therapy – Prostate subscales over time by ZA. (a) Physical well-being; (b) social well-being; (c) emotional well-being; (d) functional well-being; (e) prostate cancer; and (f) FACT-P.

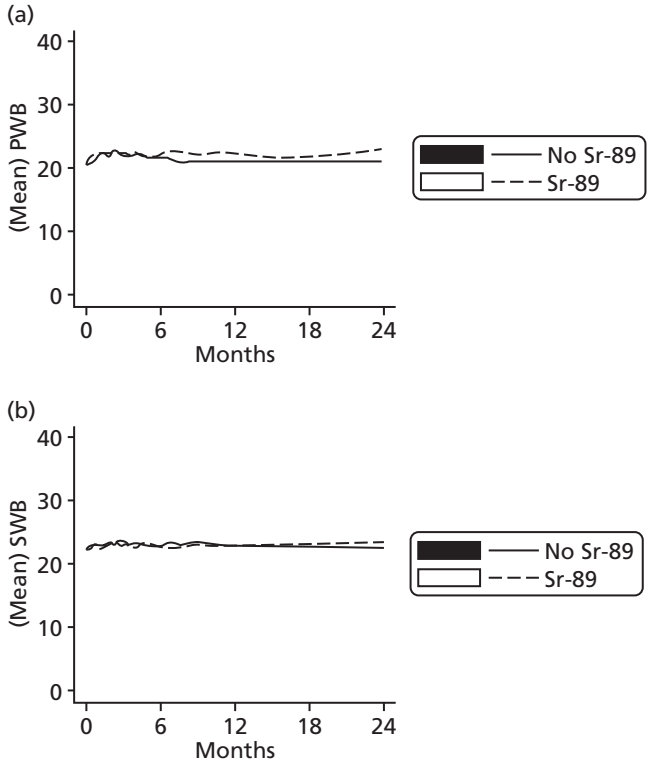


FIGURE 29 Functional Assessment of Cancer Therapy – Prostate subscale over time by Sr-89. (a) Physical well-being; (b) social well-being; (c) emotional well-being; (d) functional well-being; (e) prostate cancer; and (f) FACT-P. (*continued*)

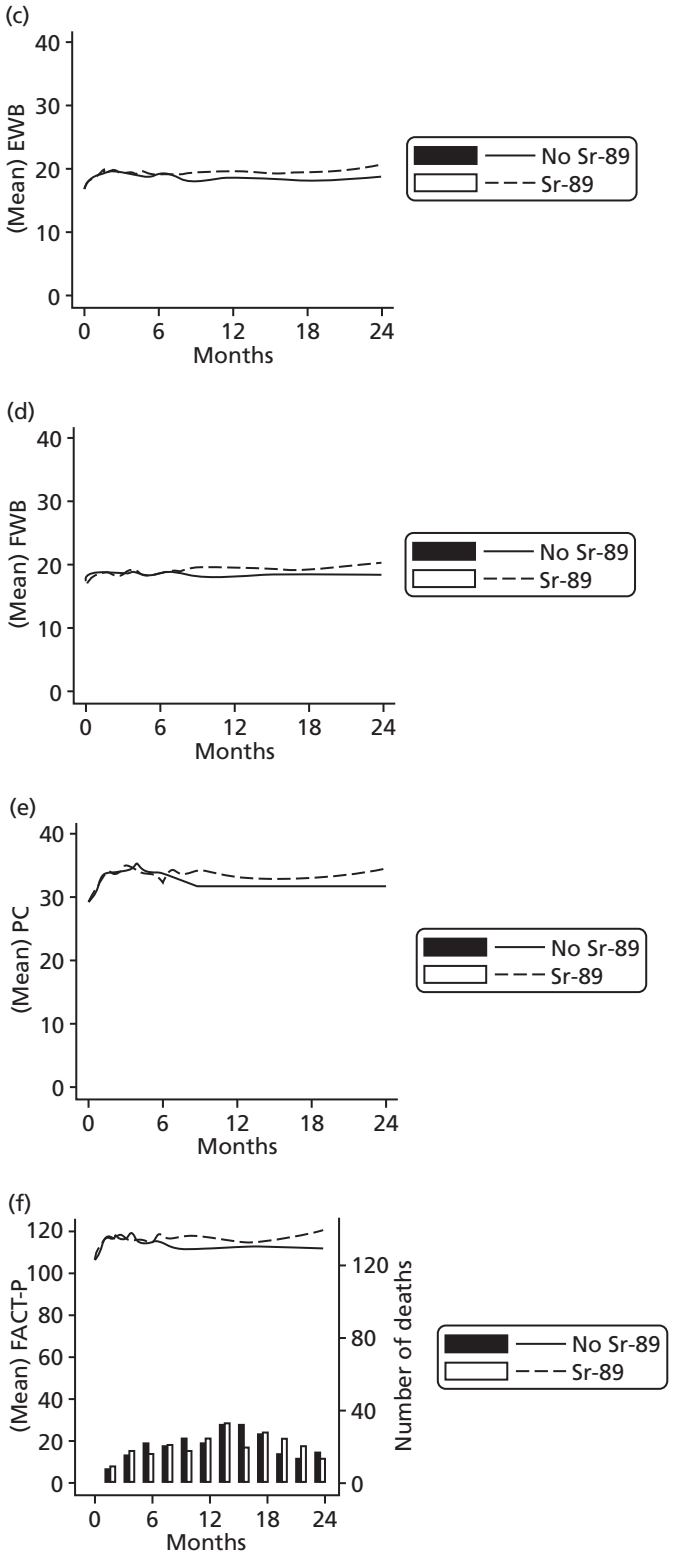


FIGURE 29 Functional Assessment of Cancer Therapy – Prostate subscale over time by Sr-89. (a) Physical well-being; (b) social well-being; (c) emotional well-being; (d) functional well-being; (e) prostate cancer; and (f) FACT-P.

As seen previously, there is an increased QoL in the first 2 months. However, there appears to be no difference between the Sr-89 comparison groups in terms of social well-being, and this has contributed to the much reduced differences observed in the overall FACT-P scale. *Figures 30* and *31* show the same six graphs, but they also split by SRE severity.

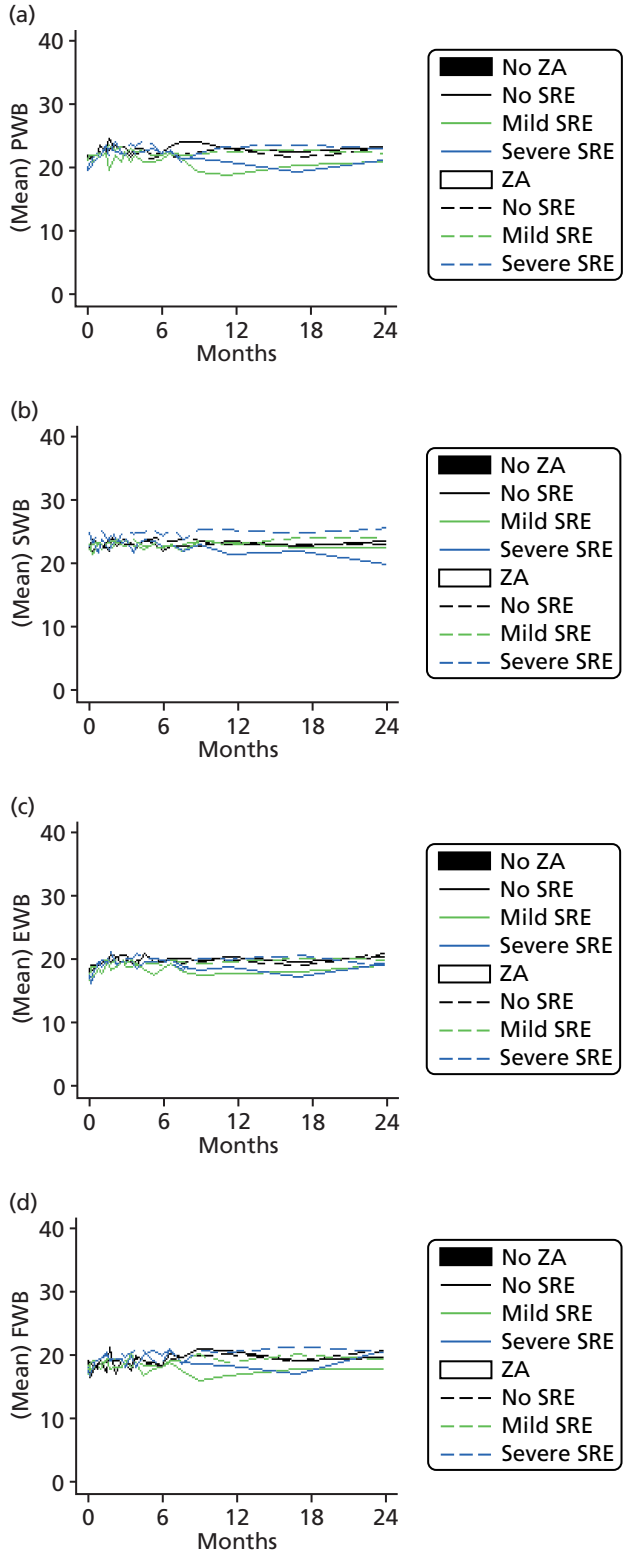


FIGURE 30 Functional Assessment of Cancer Therapy – Prostate subscale over time by SRE severity and ZA. (a) Physical well-being; (b) social well-being; (c) emotional well-being; (d) functional well-being; (e) prostate cancer; and (f) FACT-P. (*continued*)

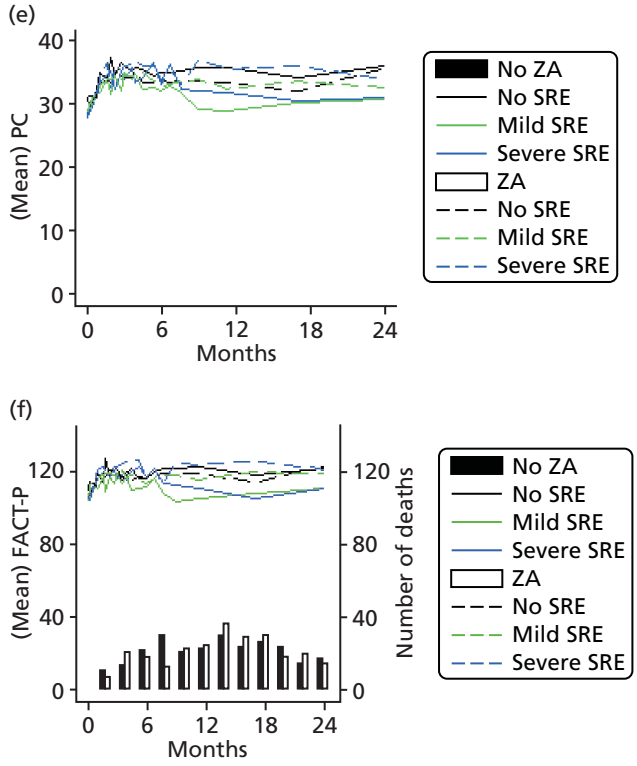


FIGURE 30 Functional Assessment of Cancer Therapy – Prostate subscale over time by SRE severity and ZA. (a) Physical well-being; (b) social well-being; (c) emotional well-being; (d) functional well-being; (e) prostate cancer; and (f) FACT-P.

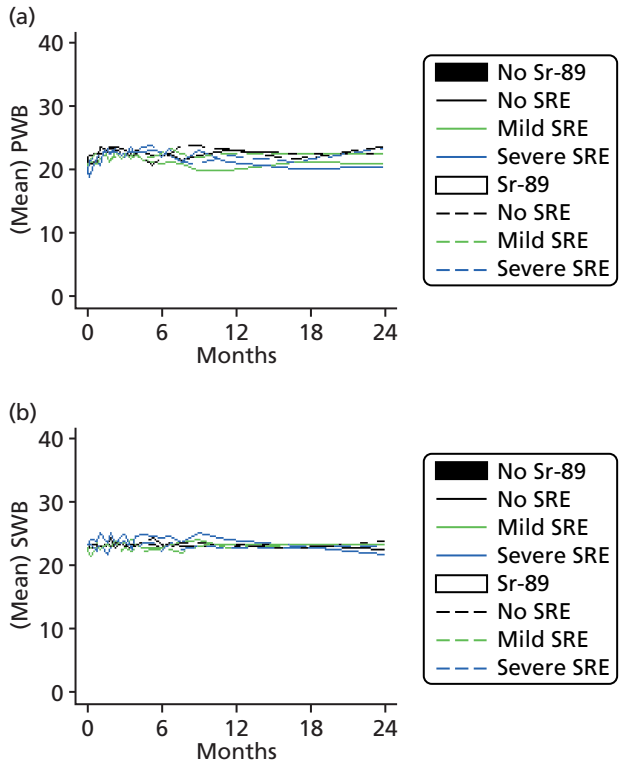


FIGURE 31 Functional Assessment of Cancer Therapy – Prostate subscale over time by SRE severity and Sr-89. (a) Physical well-being; (b) social well-being; (c) emotional well-being; (d) functional well-being; (e) prostate cancer; and (f) FACT-P. (*continued*)

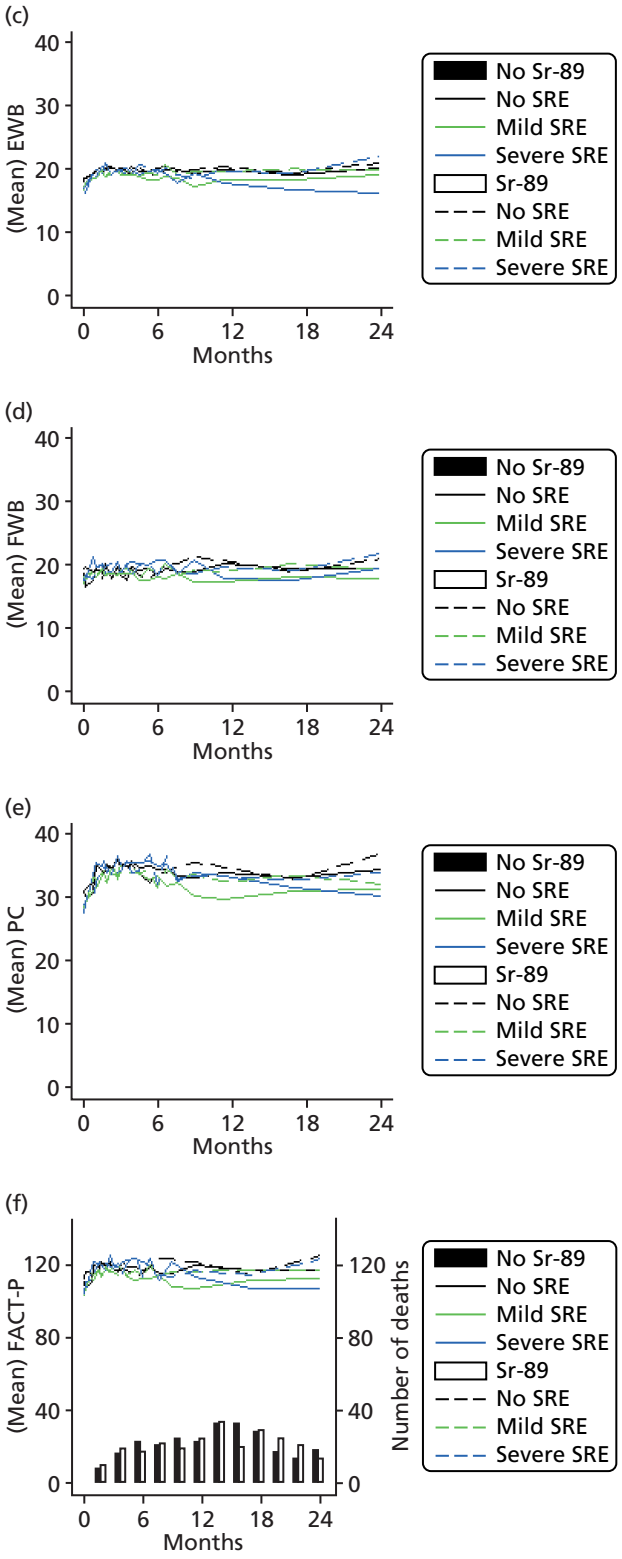


FIGURE 31 Functional Assessment of Cancer Therapy – Prostate subscale over time by SRE severity and Sr-89. (a) Physical well-being; (b) social well-being; (c) emotional well-being; (d) functional well-being; (e) prostate cancer; and (f) FACT-P.

European Quality of Life 5-Dimensions

Gains in QALYS measured using the three methods are detailed in *Table 39*, split by Sr-89 and ZA.

These findings again support the previous QoL investigations in that no difference between comparison groups is apparent. The three different methods of calculating QALYs do affect the estimates, but the differences between the groups remained consistent. *Figure 32* shows the actual returned values of the EQ-5D over time split by SRE severity and ZA.

The increase in QoL in the first 2 months is again present. *Figure 33* is the same as *Figure 32*, but split by Sr-89.

TABLE 39 Quality-adjusted life-years by comparison groups

QALYs	No ZA (*N* = 357)	ZA (*N* = 350)	No Sr-89 (*N* = 357)	Sr-89 (*N* = 350)
Conservative				
n	357	350	357	350
Mean QALYs gained (SD)	0.8 (0.6)	0.8 (0.6)	0.8 (0.6)	0.8 (0.6)
Range	–0.2 to 4.2	–0.1 to 3.6	–0.1 to 4.2	–0.2 to 4.1
Standard				
n	357	350	357	350
Mean QALYs gained (SD)	0.9 (0.7)	0.9 (0.7)	0.9 (0.7)	0.9 (0.7)
Range	–0.2 to 4.3	–0.1 to 3.6	–0.1 to 4.3	–0.2 to 4.1
Optimistic				
n	357	350	357	350
Mean QALYs gained (SD)	1.2 (1.1)	1.2 (1.1)	1.1 (1.1)	1.2 (1.1)
Range	–0.2 to 5.2	–0.4 to 4.6	–0.1 to 5.2	–0.4 to 4.7

SD, standard deviation.

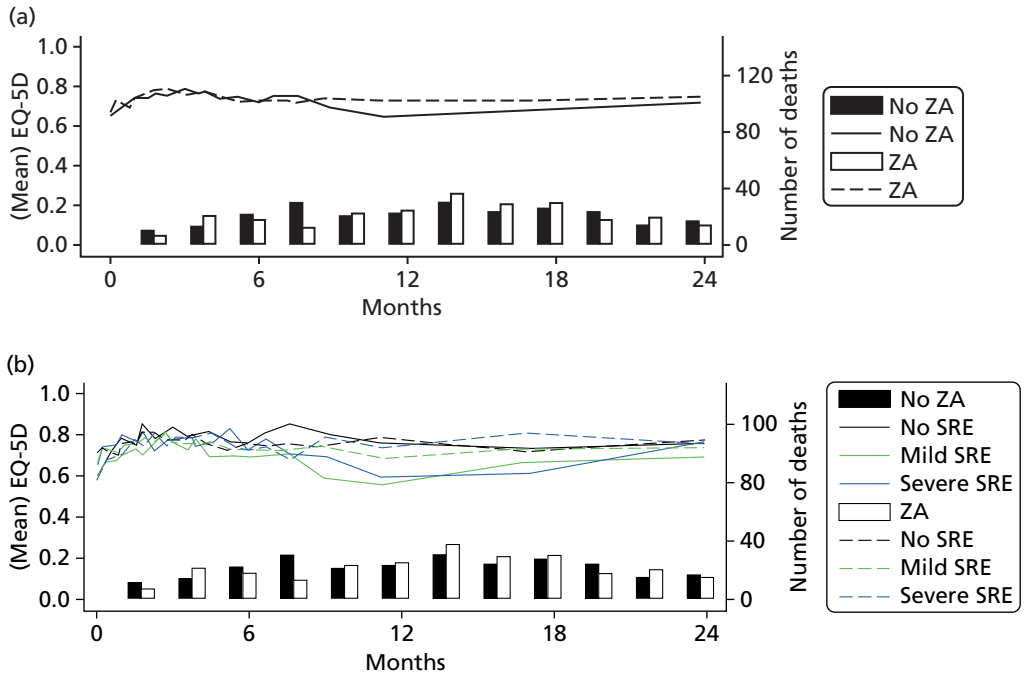


FIGURE 32 European Quality of Life 5-Dimensions over time by ZA and SRE Severity. (a) EQ-5D by ZA; and (b) EQ-5D by worst SRE and ZA.

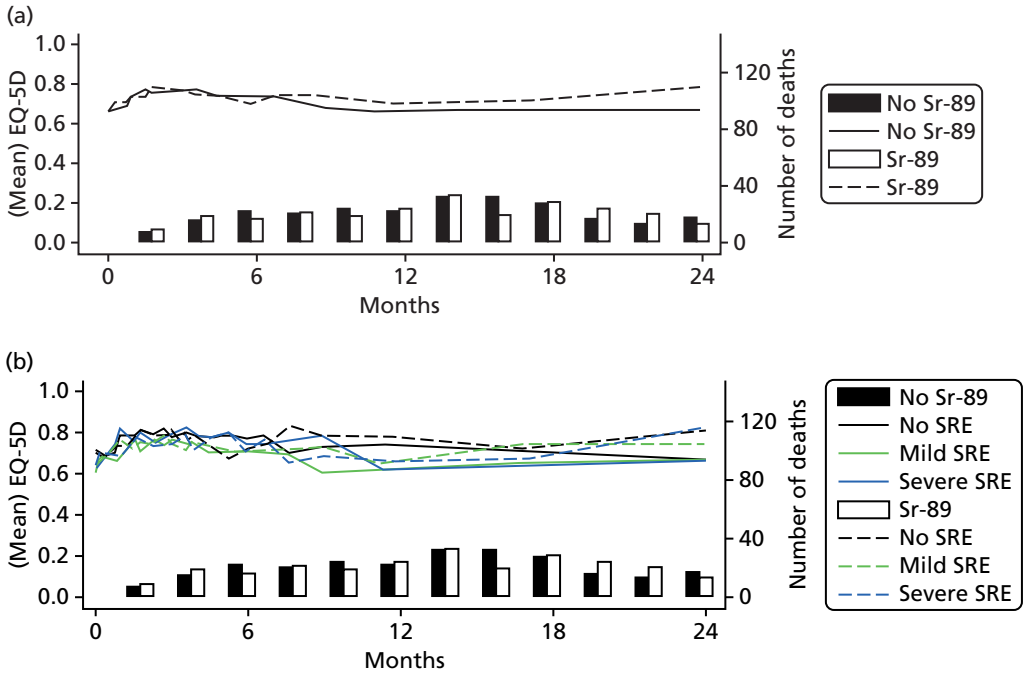


FIGURE 33 European Quality of Life 5-Dimensions over time by Sr-89 and SRE severity. (a) EQ-5D by Sr-89; and (b) EQ-5D by worst SRE and Sr-89.

Quality-adjusted survival

Quality-adjusted survival within 2 years split by the comparison groups is detailed in *Table 40*.

Adjusting for QoL does not change the conclusions of the overall survival analysis alone. There were no statistically or clinically meaningful differences between either comparison group. The 2-year quality-adjusted survival is approximately 1 year in all comparison arms, which is 4 to 6 months shorter than the survival analysis alone. *Figures 34* and *35* illustrate the QoL function, the survival function and the integrated quality survival product for the two comparison groups.

The Sr-89 integrated survival product does show a slight difference, with those receiving Sr-89 gaining approximately one additional quality-adjusted survival month.

TABLE 40 Quality-adjusted survival at 2 years by comparison groups

	No ZA	ZA	No Sr-89	Sr-89
Comparitor	Estimate (95% CI)	Estimate (95% CI)	Estimate (95% CI)	Estimate (95% CI)
Mean life-years gained (within 2 years)	1.47 (1.34 to 1.58)	1.42 (1.34 to 1.59)	1.38 (1.30 to 1.52)	1.51 (1.39 to 1.59)
Quality-adjusted survival (within 2 years)	1.00 (0.93 to 1.10)	1.04 (0.98 to 1.10)	0.97 (0.991 to 1.03)	1.05 (0.99 to 1.12)

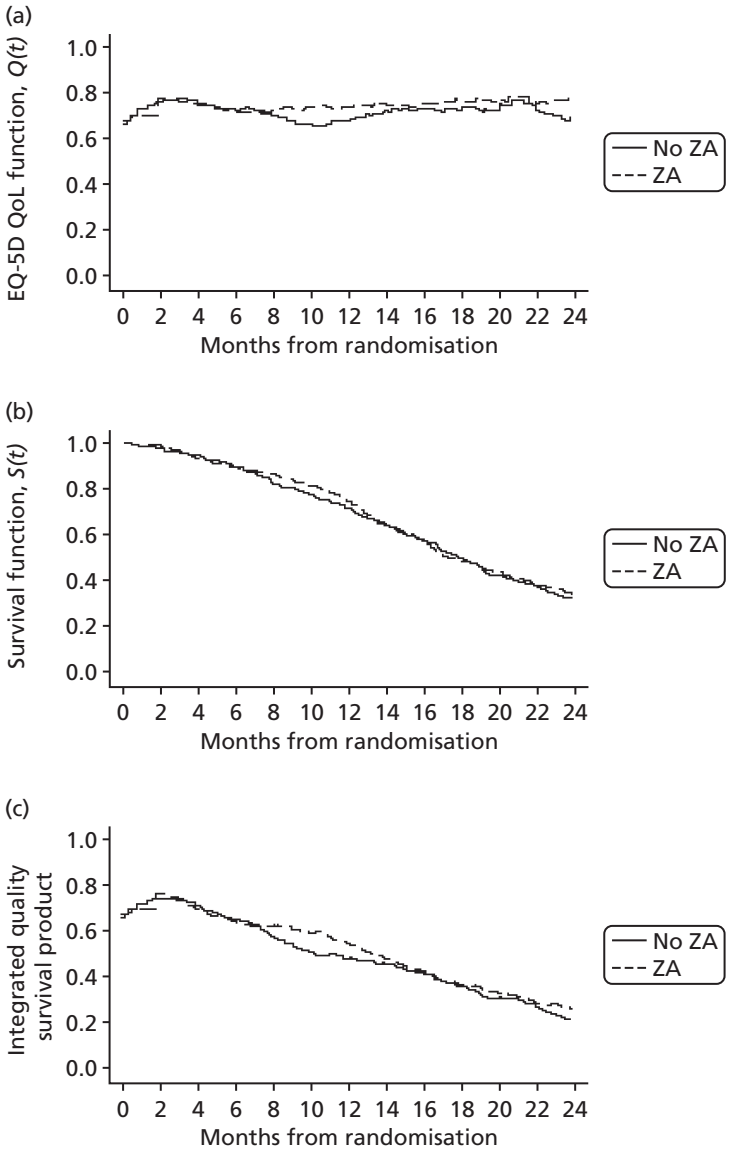


FIGURE 34 Quality-adjusted survival split by ZA group. (a) EQ-5D QoL function, $Q(t)$; (b) survival function, $S(t)$; and (c) integrated quality survival product.

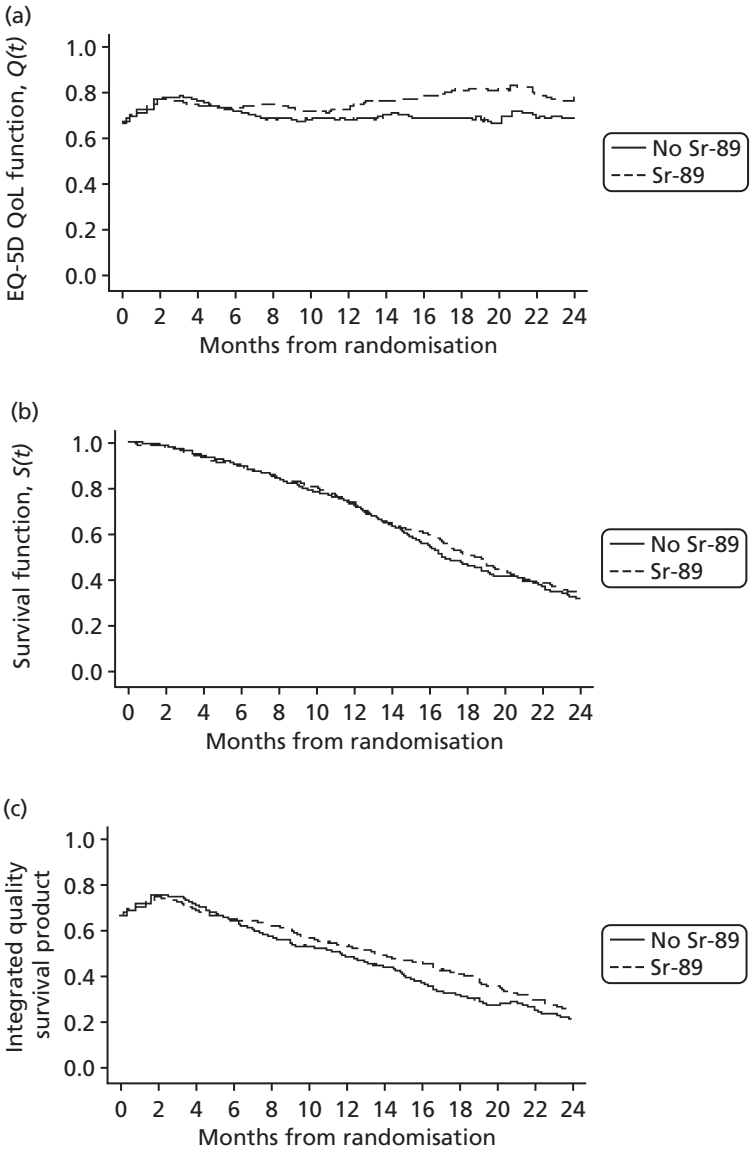


FIGURE 35 Quality-adjusted survival split by Sr-89 group. (a) EQ-5D QoL function, $Q(t)$; (b) survival function, $S(t)$; and (c) integrated quality survival product.

Adverse events

Timing of events

In total, 493 grade 3 or 4 adverse events (AEs) were reported. In addition, 313 events without a grade were reported and 161 without a start date were reported, making it impossible to determine whether these events occurred on- or off-treatment.

Additionally, there were 178 (24%) patients who reported no grade 3 or 4 AEs, while 27 patients reported experiencing AEs but did not receive any treatment. *Table 41* shows the grading and timing of all AEs.

Tables 42 and *43* show the percentages of patients at each time point who reported at least one grade 3 or 4 event, split by randomisation arm and comparison group.

Tables 41–43 indicate that there was a peak in adverse events at cycle 6. This may have been a function of increased scrutiny at this time point to ensure that patients were well enough to receive additional treatment, which was particularly important for those randomised to receive Sr-89.

TABLE 41 Adverse event timings

	Grade 3 (*N* = 447)		Grade 4 (*N* = 46)		Missing (*N* = 313)		Overall (*N* = 806)	
Time point	*n*	%	*n*	%	*n*	%	*n*	%
Pre-treatment	13	2.9	4	8.7	8	2.6	25	3.1
Cycle 1	101	22.6	11	23.9	38	12.1	150	18.6
Cycle 2	55	12.3	10	21.7	23	7.3	88	10.9
Cycle 3	52	11.6	5	10.9	18	5.8	75	9.3
Cycle 4	31	6.9	5	10.9	16	5.1	52	6.5
Cycle 5	38	8.5	3	6.5	7	2.2	48	6.0
Cycle 6	81	18.1	4	8.7	54	17.3	139	17.2
Cycle 7	18	4.0	2	4.3	2	0.6	22	2.7
Cycle 8	10	2.2	0	0.0	1	0.3	11	1.4
Cycle 9	5	1.1	0	0.0	4	1.3	9	1.1
Cycle 10	3	0.7	1	2.2	0	0.0	4	0.5
Follow-up 1	6	1.3	0	0.0	5	1.6	11	1.4
Follow-up 2	1	0.2	1	2.2	0	0.0	2	0.2
Follow-up 3	3	0.7	0	0.0	1	0.3	4	0.5
Follow-up 4	5	1.1	0	0.0	0	0.0	5	0.6
Unknown	25	5.6	0	0.0	136	43.5	161	20.0
Total	447	100.0	46	100.0	313	100.0	806	100.0

TABLE 42 Percentages of patients experiencing grade 3 or 4 AEs

Time point	Docetaxel (%)	Docetaxel + ZA (%)	Docetaxel + Sr-89 (%)	Docetaxel + ZA + Sr-89 (%)	Overall (%)
Cycle 1	14.0	17.2	12.7	17.6	15.4
Cycle 2	12.8	4.8	8.6	11.1	9.4
Cycle 3	7.1	8.6	11.4	7.2	8.6
Cycle 4	4.4	5.1	10.5	3.2	5.8
Cycle 5	7.4	6.1	6.3	8.1	7.0
Cycle 6	10.2	13.6	17.7	22.6	16.1
Cycle 7	20.0	10.5	6.1	3.9	9.9
Cycle 8	2.6	3.8	4.5	11.4	5.6
Cycle 9	2.9	9.3	0	0	3.2
Cycle 10	3.8	5.9	2.9	0	3.1
Follow-up 1	0	3.2	0.7	0	1.0
Follow-up 2	0.7	0	0.7	0	0.3
Follow-up 3	0	0.7	1.6	0	0.6
Follow-up 4	0.9	3.4	0	0	1.1

TABLE 43 Percentage of patients with grade 3 or 4 AEs

Time point	No ZA (%)	ZA (%)	No Sr-89 (%)	Sr-89 (%)
Cycle 1	13.4	17.4	15.6	15.2
Cycle 2	10.7	8.0	9.0	9.8
Cycle 3	9.2	8.0	7.8	9.3
Cycle 4	7.4	4.2	4.8	6.8
Cycle 5	6.8	7.1	6.8	7.2
Cycle 6	14.0	18.2	11.9	20.2
Cycle 7	12.8	7.4	14.7	5.0
Cycle 8	3.7	7.2	3.3	8.0
Cycle 9	1.4	5.0	6.5	0
Cycle 10	3.3	2.9	5.0	1.4
Follow-up 1	0.3	1.6	1.6	0.3
Follow-up 2	0.7	0	0.3	0.4
Follow-up 3	0.8	0.4	0.4	0.8
Follow-up 4	0.5	1.7	2.2	0

Grade and number of adverse events

Figures 36 and *37* show the grade and number of AEs over time, split by comparisons. The graphs show that grade 3 and 4 AEs peak at cycle 1 and cycle 6. There appear to be additional events associated with Sr-89 at cycle 6, which makes sense, as this would include the time during which Sr-89 is administered, but there is no evidence to suggest that these effects are long-lasting. In terms of ZA, increased numbers of events are seen at both peaks. However, it is worth noting that the magnitude of these differences is only 10 individual events.

Figure 38 shows the time and type of any AE where at least five or more instances were observed at one time point. This is split by comparison groups.

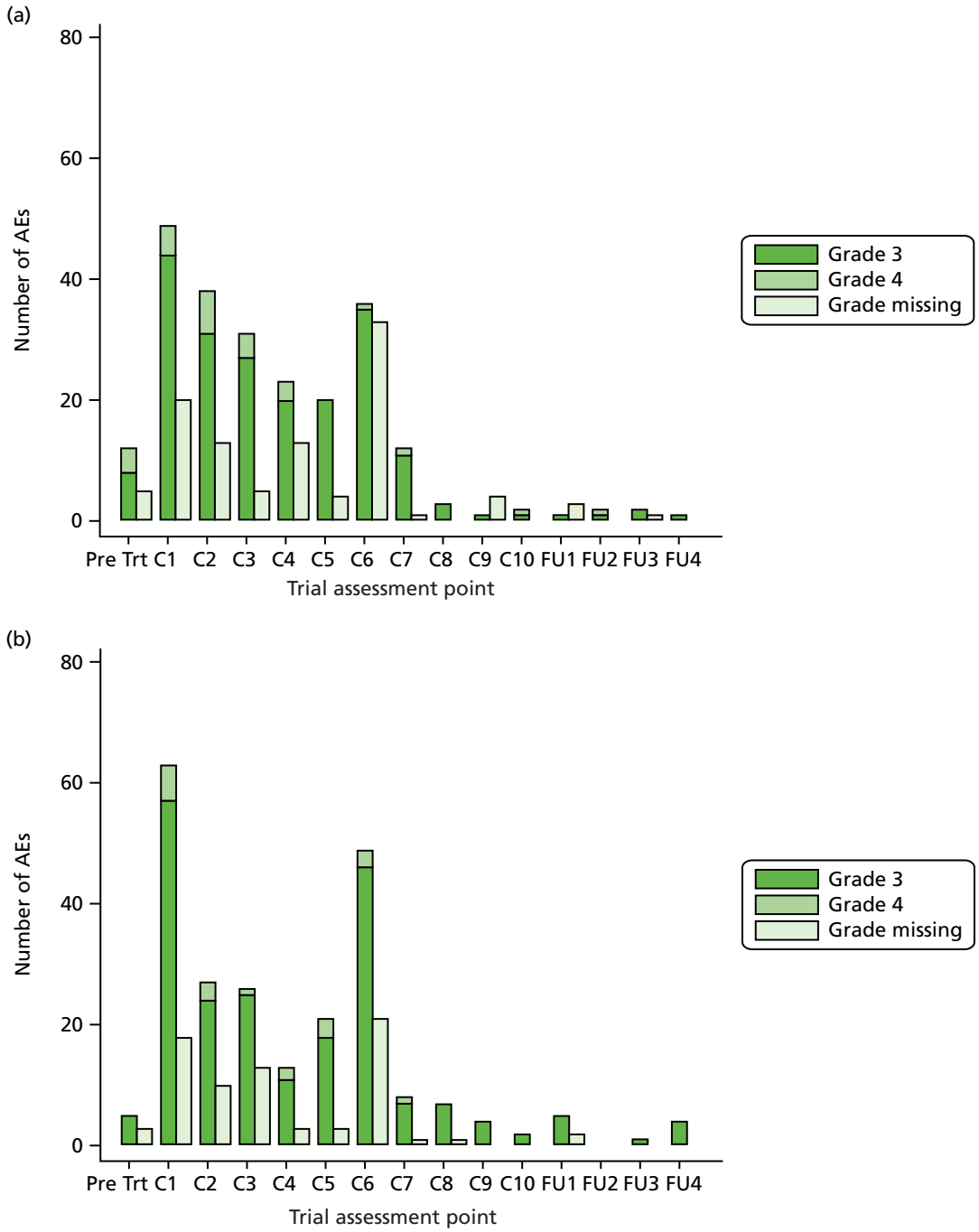


FIGURE 36 Grade and number of AEs over time by ZA comparison. (a) No ZA; and (b) ZA.

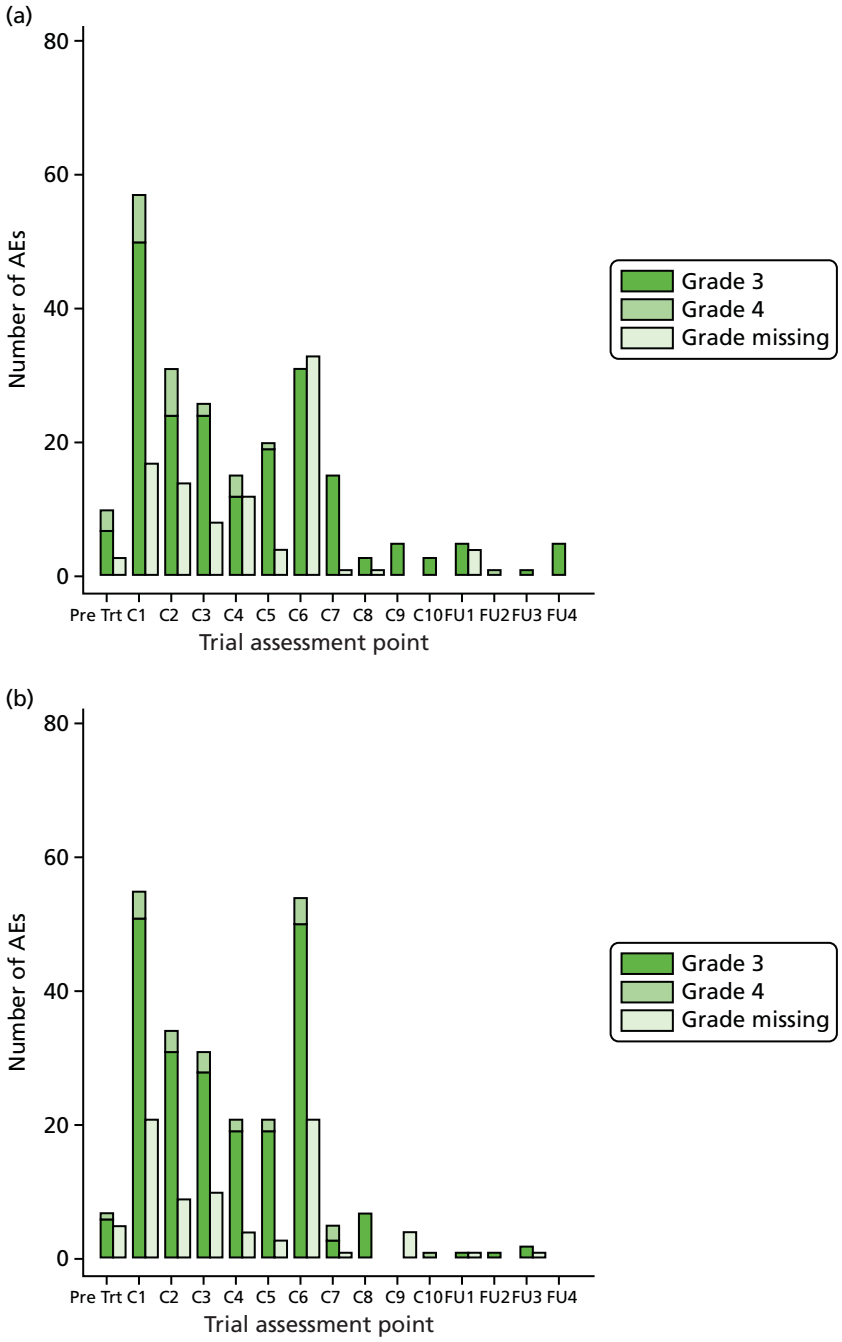


FIGURE 37 Grade and number of AEs over time by Sr-89 comparison. (a) No Sr-89; and (b) Sr-89.

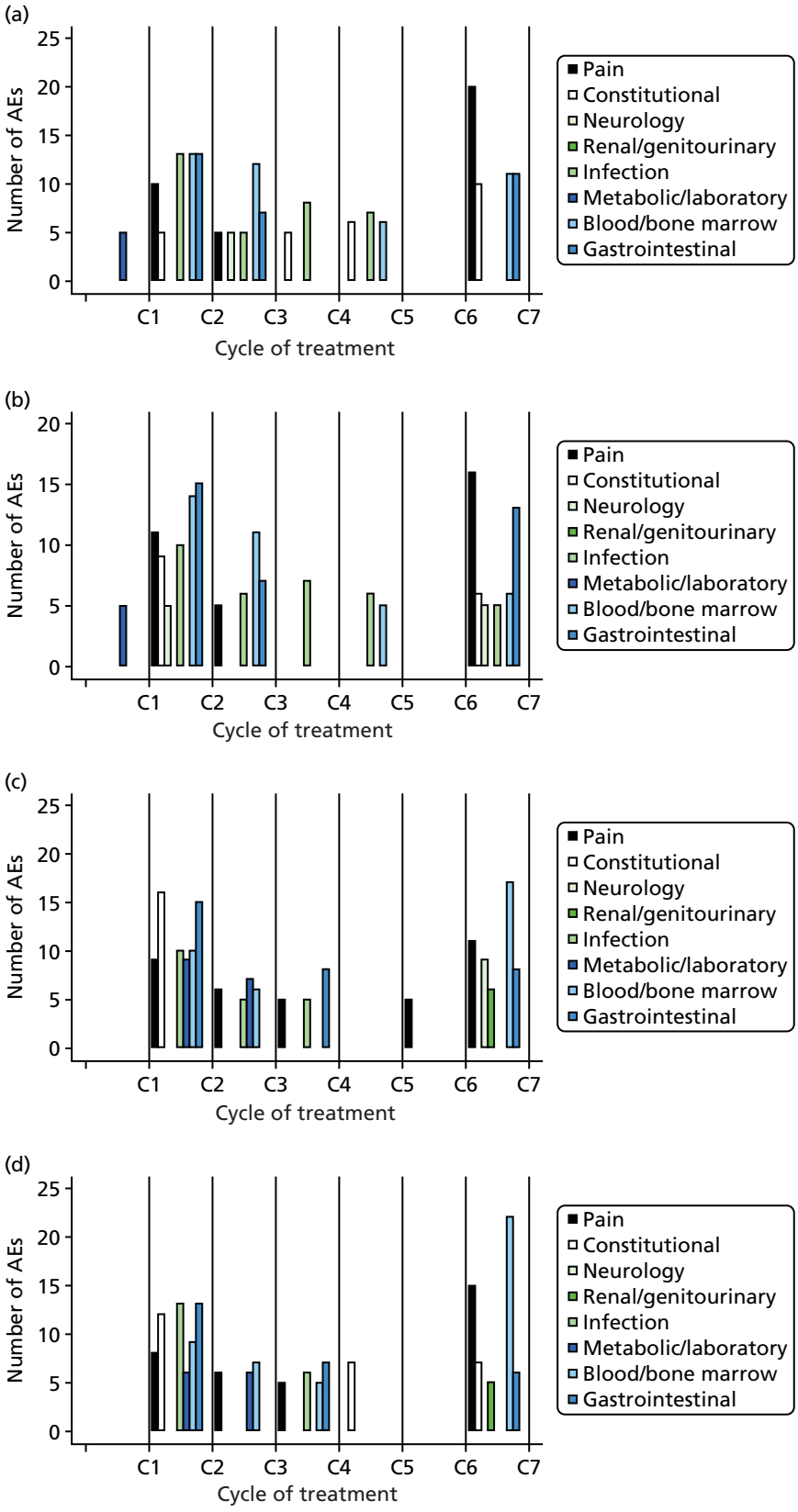


FIGURE 38 Frequency of AEs over time. (a) No ZA; (b) no Sr-89; (c) ZA; and (d) Sr-89.

Adverse event symptoms

Tables 44–46 show the adverse event symptoms reported by randomisation arm separately for grades 3 and 4 and missing grades.

The most common grade 4 events were infection- and blood/bone marrow-related. However, it did not appear to be the case that the combined arm containing both ZA and Sr-89 was experiencing more grade 4 AEs.

TABLE 44 Symptoms of grade 3 AEs

Category as defined in *Common Terminology Criteria for Adverse Events, version 3*[54]	Docetaxel (*N* = 106)		Docetaxel + ZA (*N* = 109)		Docetaxel + Sr-89 (*N* = 117)		Docetaxel + ZA + Sr-89 (*N* = 115)		Overall (*N* = 447)	
	n	%	*n*	%	*n*	%	*n*	%	*n*	%
Pulmonary/upper respiratory	8	7.5	3	2.8	0	0.0	0	0.0	11	2.5
Pain	16	15.1	10	9.2	16	13.7	11	9.6	53	11.9
Haemorrhage/bleeding	0	0.0	0	0.0	1	0.9	1	0.9	2	0.4
Ocular/visual	0	0.0	0	0.0	0	0.0	1	0.9	1	0.2
Constitutional symptoms	13	12.3	10	9.2	20	17.1	12	10.4	55	12.3
Allergy/immunology	3	2.8	1	0.9	0	0.0	0	0.0	4	0.9
Musculoskeletal/soft tissue	1	0.9	4	3.7	5	4.3	2	1.7	12	2.7
Neurology	7	6.6	10	9.2	8	6.8	5	4.3	30	6.7
Lymphatics	4	3.8	2	1.8	2	1.7	9	7.8	17	3.8
Renal/genitourinary	0	0.0	5	4.6	2	1.7	7	6.1	14	3.1
Dermatology/skin	6	5.7	7	6.4	6	5.1	2	1.7	21	4.7
Vascular	0	0.0	1	0.9	1	0.9	4	3.5	6	1.3
Infection	16	15.1	15	13.8	12	10.3	12	10.4	55	12.3
Metabolic/laboratory	9	8.5	12	11.0	11	9.4	15	13.0	47	10.5
Blood/bone marrow	13	12.3	20	18.3	21	17.9	17	14.8	71	15.9
Cardiac general	0	0.0	0	0.0	2	1.7	0	0.0	2	0.4
Sexual/reproductive function	0	0.0	1	0.9	0	0.0	0	0.0	1	0.2
Cardiac arrhythmia	0	0.0	0	0.0	0	0.0	2	1.7	2	0.4
Syndromes	0	0.0	0	0.0	1	0.9	1	0.9	2	0.4
Endocrine	0	0.0	0	0.0	0	0.0	1	0.9	1	0.2
Gastrointestinal	10	9.4	8	7.3	9	7.7	13	11.3	40	8.9
Total	106	100.0	109	100.0	117	100.0	115	100.0	447	100.0

TABLE 45 Symptoms of grade 4 AEs

Category as defined in *Common Terminology Criteria for Adverse Events, version 3*[54]	Docetaxel (*N* = 15)		Docetaxel + ZA (*N* = 9)		Docetaxel + Sr-89 (*N* = 12)		Docetaxel + ZA + Sr-89 (*N* = 10)		Overall (*N* = 46)	
	n	%	*n*	%	*n*	%	*n*	%	*n*	%
Pulmonary/upper respiratory	1	6.7	0	0.0	0	0.0	0	0.0	1	2.2
Pain	0	0.0	0	0.0	0	0.0	1	10.0	1	2.2
Neurology	0	0.0	0	0.0	1	8.3	1	10.0	2	4.3
Vascular	1	6.7	3	33.3	0	0.0	0	0.0	4	8.7
Infection	5	33.3	1	11.1	4	33.3	2	20.0	12	26.1
Metabolic/laboratory	1	6.7	2	22.2	1	8.3	0	0.0	4	8.7
Blood/bone marrow	5	33.3	3	33.3	6	50.0	6	60.0	20	43.5
Cardiac general	2	13.3	0	0.0	0	0.0	0	0.0	2	4.3
Total	15	100.0	9	100.0	12	100.0	10	100.0	46	100.0

TABLE 46 Symptoms of AEs of unknown grade

Category as defined in *Common Terminology Criteria for Adverse Events, version 3*[54]	Docetaxel (*N* = 91)		Docetaxel + ZA (*N* = 73)		Docetaxel + Sr-89 (*N* = 78)		Docetaxel + ZA + Sr-89 (*N* = 71)		Overall (*N* = 313)	
	n	%	*n*	%	*n*	%	*n*	%	*n*	%
Pulmonary/upper respiratory	2	2.5	1	1.8	2	3.2	3	5.5	8	3.1
Pain	22	27.5	14	25.0	15	23.8	14	25.5	65	25.6
Haemorrhage/bleeding	1	1.3	0	0.0	0	0.0	0	0.0	1	0.4
Ocular/visual	0	0.0	0	0.0	1	1.6	0	0.0	1	0.4
Constitutional symptoms	6	7.5	9	16.1	5	7.9	3	5.5	23	9.1
Allergy/immunology	1	1.3	0	0.0	0	0.0	0	0.0	1	0.4
Musculoskeletal/soft tissue	4	5.0	5	8.9	2	3.2	3	5.5	14	5.5
Neurology	2	2.5	1	1.8	5	7.9	3	5.5	11	4.3
Lymphatics	4	5.0	4	7.1	4	6.3	2	3.6	14	5.5
Renal/genitourinary	0	0.0	2	3.6	2	3.2	2	3.6	6	2.4
Dermatology/skin	2	2.5	5	8.9	8	12.7	4	7.3	19	7.5
Infection	5	6.3	3	5.4	2	3.2	2	3.6	12	4.7
Metabolic/laboratory	0	0.0	0	0.0	0	0.0	2	3.6	2	0.8
Blood/bone marrow	4	5.0	3	5.4	2	3.2	4	7.3	13	5.1
Cardiac general	1	1.3	0	0.0	0	0.0	0	0.0	1	0.4
Cardiac arrhythmia	0	0.0	0	0.0	1	1.6	0	0.0	1	0.4
Syndromes	3	3.8	0	0.0	0	0.0	0	0.0	3	1.2
Endocrine	0	0.0	0	0.0	2	3.2	0	0.0	2	0.8
Gastrointestinal	22	27.5	9	16.1	12	19.0	13	23.6	56	22.0
Secondary malignancy	1	1.3	0	0.0	0	0.0	0	0.0	1	0.4
Missing	11	–	17	–	15	–	16	–	59	–
Total	80	100.0	56	100.0	63	100.0	55	100.0	254	100.0

Serious adverse events

In total, 583 SAEs were reported, with 1064 associated symptoms, relating to 373 (49%) patients. *Tables 47* and *48* show the categorisation of the 583 SAEs by both randomisation arm and comparison group.

Tables 49 and *50* show the number of SAEs experienced per patient, split by randomisation arm and comparison group.

Approximately 50% of patients in each comparison group experienced at least one SAE, with approximately 20% going on to have multiple SAEs.

TABLE 47 Serious adverse event categorisations by randomisation arm

	Docetaxel (*N* = 133)		Docetaxel + ZA (*N* = 164)		Docetaxel + Sr-89 (*N* = 146)		Docetaxel + ZA + Sr-89 (*N* = 140)		Overall (*N* = 583)	
SAE categorisation	*n*	%	*n*	%	*n*	%	*n*	%	*n*	%
Unrelated SAE	56	42.1	96	58.5	67	45.9	67	47.9	286	49.1
SAR	73	54.9	65	39.6	73	50.0	65	46.4	276	47.3
Non-fatal/life-threatening SUSAR	1	0.8	1	0.6	3	2.1	1	0.7	6	1.0
Fatal/life-threatening SUSAR	3	2.3	2	1.2	3	2.1	7	5.0	15	2.6
Total	133	100.0	164	100.0	146	100.0	140	100.0	583	100.0

SAR, serious adverse reaction; SUSAR, suspected unexpected serious adverse reaction.

TABLE 48 Serious adverse event categorisations by ZA and Sr-89 comparison

	No ZA (*N* = 279)		ZA (*N* = 304)		No Sr-89 (*N* = 297)		Sr-89 (*N* = 286)	
SAE categorisation	*n*	%	*n*	%	*n*	%	*n*	%
Unrelated SAE	123	44.1	163	53.6	152	51.2	134	46.9
SAR	146	52.3	130	42.8	138	46.5	138	48.3
Non-fatal/life-threatening SUSAR	4	1.4	2	0.7	2	0.7	4	1.4
Fatal/life-threatening SUSAR	6	2.2	9	3.0	5	1.7	10	3.5
Total	279	100.0	304	100.0	297	100.0	286	100.0

SAR, serious adverse reaction; SUSAR, suspected unexpected serious adverse reaction.

TABLE 49 Number of SAEs per patient by randomisation arm

	Docetaxel (*N* = 191)		Docetaxel + ZA (*N* = 188)		Docetaxel + Sr-89 (*N* = 190)		Docetaxel + ZA + Sr-89 (*N* = 188)		Overall (*N* = 757)	
Number of SAEs per patient	*n*	%	*n*	%	*n*	%	*n*	%	*n*	%
1	48	25	72	38	64	34	49	26	233	31
2	24	13	17	9	23	12	24	13	88	12
3	11	6	11	6	5	3	11	6	38	5
4	1	0	5	3	4	2	1	< 1	11	1
5	0	0	1	< 1	1	< 1	0	0	2	< 1
6	0	0	0	0	0	0	1	< 1	1	< 1
Patients with ≥ 1 SAE	84	44	106	56	97	51	86	46	373	49

TABLE 50 Number of SAEs per patient by ZA and Sr-89 comparison group

	No ZA (*N* = 381)		ZA (*N* = 376)		No Sr-89 (*N* = 379)		Sr-89 (*N* = 378)	
Number of SAEs per patient	*n*	%	*n*	%	*n*	%	*n*	%
1	112	30	121	32	120	32	113	30
2	47	12	41	11	41	11	47	12
3	16	4	22	6	22	6	16	4
4	5	1	6	2	6	1	5	1
5	1	< 1	1	< 1	1	< 1	1	< 1
6	0	0	1	< 1	0	0	1	< 1
Patients with ≥ 1 SAE	181	47	192	51	190	50	183	48

Reasons for serious adverse events

Tables 51 and *52* show the reasons for SAEs split by both randomisation arm and comparison groups.

By far the most common reason for reporting an SAE was hospitalisation, which alone accounted for 80% of all SAEs.

TABLE 51 Serious adverse event reasons by randomisation arm

	Docetaxel (*N* = 133)		Docetaxel + ZA (*N* = 164)		Docetaxel + Sr-89 (*N* = 146)		Docetaxel + ZA + Sr-89 (*N* = 140)		Overall (*N* = 583)	
New reason	*n*	%	*n*	%	*n*	%	*n*	%	*n*	%
Death	1	0.8	7	4.3	8	5.5	9	6.4	25	4.3
Death and disability	0	0.0	1	0.6	0	0.0	0	0.0	1	0.2
Death and hospitalisation	4	3.0	5	3.0	7	4.8	9	6.4	25	4.3
Death and other	0	0.0	0	0.0	0	0.0	1	0.7	1	0.2
Death, hospitalisation and disability	1	0.8	0	0.0	0	0.0	0	0.0	1	0.2
Death, life-threatening and hospitalisation	1	0.8	2	1.2	0	0.0	2	1.4	5	0.9
Death, life-threatening, hospitalisation and other	0	0.0	0	0.0	0	0.0	1	0.7	1	0.2
Disability	0	0.0	2	1.2	1	0.7	1	0.7	4	0.7
Hospitalisation	115	86.5	124	75.6	117	80.1	111	79.3	467	80.1
Hospitalisation and disability	3	2.3	4	2.4	1	0.7	3	2.1	11	1.9
Hospitalisation and other	2	1.5	2	1.2	2	1.4	0	0.0	6	1.0
Hospitalisation, disability and other	1	0.8	1	0.6	0	0.0	0	0.0	2	0.3
Life-threatening	0	0.0	1	0.6	1	0.7	0	0.0	2	0.3
Life-threatening and hospitalisation	3	2.3	12	7.3	4	2.7	3	2.1	22	3.8
New primary cancer	1	0.8	0	0.0	0	0.0	0	0.0	1	0.2
Other	1	0.8	3	1.8	5	3.4	0	0.0	9	1.5
Total	133	100.0	164	100.0	146	100.0	140	100.0	583	100.0

TABLE 52 Serious adverse event reasons by ZA and Sr-89 comparison group

	No ZA (*N* = 279)		ZA (*N* = 304)		No Sr-89 (*N* = 297)		Sr-89 (*N* = 286)	
Reason	*n*	%	*n*	%	*n*	%	*n*	%
Death	9	3.2	16	5.3	8	2.7	17	5.9
Death and disability	0	0.0	1	0.3	1	0.3	0	0.0
Death and hospitalisation	11	3.9	14	4.6	9	3.0	16	5.6
Death and other	0	0.0	1	0.3	0	0.0	1	0.3
Death, hospitalisation and disability	1	0.4	0	0.0	1	0.3	0	0.0
Death, life-threatening and hospitalisation	1	0.4	4	1.3	3	1.0	2	0.7
Death, life-threatening, hospitalisation and other	0	0.0	1	0.3	0	0.0	1	0.3
Disability	1	0.4	3	1.0	2	0.7	2	0.7
Hospitalisation	232	83.2	235	77.3	239	80.5	228	79.7
Hospitalisation and disability	4	1.4	7	2.3	7	2.4	4	1.4
Hospitalisation and other	4	1.4	2	0.7	4	1.3	2	0.7
Hospitalisation, disability and other	1	0.4	1	0.3	2	0.7	0	0.0
Life-threatening	1	0.4	1	0.3	1	0.3	1	0.3
Life-threatening and hospitalisation	7	2.5	15	4.9	15	5.1	7	2.4
New primary cancer	1	0.4	0	0.0	1	0.3	0	0.0
Other	6	2.2	3	1.0	4	1.3	5	1.7
Total	279	100.0	304	100.0	297	100.0	286	100.0

Serious adverse event symptoms by serious adverse event categorisation by randomisation arm

Multiple symptoms were associated with each SAE in a total of 1064 reported symptoms. *Tables 53* and *54* split these symptoms by type of SAE and randomisation arm.

Tables 55 and *56* split the symptoms associated with SAE by category of SAE and comparison groups.

TABLE 53 Symptoms of unrelated SAEs

Category as defined in *Common Terminology Criteria for Adverse Events, version 3*[54]	Docetaxel (*N* = 87)		Docetaxel + ZA (*N* = 154)		Docetaxel + Sr-89 (*N* = 103)		Docetaxel + ZA + Sr-89 (*N* = 120)		Overall (*N* = 464)	
	n	%	*n*	%	*n*	%	*n*	%	*n*	%
Pulmonary/upper respiratory	8	9.2	3	1.9	5	4.9	10	8.3	26	5.6
Pain	18	20.7	20	13.0	19	18.6	15	12.5	72	15.6
Haemorrhage/bleeding	1	1.1	7	4.5	3	2.9	3	2.5	14	3.0
Ocular/visual	0	0.0	4	2.6	1	1.0	0	0.0	5	1.1
Constitutional symptoms	10	11.5	10	6.5	7	6.9	6	5.0	33	7.1
Musculoskeletal/soft tissue	8	9.2	14	9.1	14	13.7	10	8.3	46	9.9
Neurology	10	11.5	13	8.4	8	7.8	9	7.5	40	8.6
Lymphatics	1	1.1	3	1.9	2	2.0	3	2.5	9	1.9
Auditory/ear	0	0.0	1	0.6	0	0.0	0	0.0	1	0.2
Renal/genitourinary	3	3.4	23	14.9	11	10.8	8	6.7	45	9.7
Dermatology/skin	0	0	1	0.6	0	0.0	1	0.8	2	0.4
Vascular	2	2.3	2	1.3	2	2.0	9	7.5	15	3.2
Surgery/intraoperative injury	0	0.0	1	0.6	0	0.0	0	0.0	1	0.2
Infection	3	3.4	8	5.2	2	2.0	10	8.3	23	5.0
Metabolic/laboratory	3	3.4	4	2.6	4	3.9	3	2.5	14	3.0
Blood/bone marrow	5	5.7	8	5.2	1	1.0	7	5.8	21	4.5
Cardiac general	2	2.3	4	2.6	3	2.9	2	1.7	11	2.4
Death	2	2.3	9	5.8	7	6.9	5	4.2	23	5.0
Cardiac arrhythmia	1	1.1	0	0.0	2	2.0	3	2.5	6	1.3
Syndromes	0	0.0	1	0.6	1	1.0	0	0.0	2	0.4
Gastrointestinal	9	10.3	18	11.7	10	9.8	16	13.3	53	11.4
Secondary malignancy	1	1.1	0	0.0	0	0.0	0	0.0	1	0.2
Missing	0	–	0	–	1	–	0	–	1	–
Total	87	100	154	100	102	100	120	100	463	100

TABLE 54 Symptoms of SAEs

Category as defined in *Common Terminology Criteria for Adverse Events, version 3*[54]	Docetaxel (*N* = 142)		Docetaxel + ZA (*N* = 133)		Docetaxel + Sr-89 (*N* = 142)		Docetaxel + ZA + Sr-89 (*N* = 131)		Overall (*N* = 548)	
	n	%	*n*	%	*n*	%	*n*	%	*n*	%
Pulmonary/upper respiratory	11	8.1	11	8.4	4	2.8	6	4.6	32	5.9
Pain	4	2.9	4	3.1	8	5.7	7	5.4	23	4.3
Haemorrhage/bleeding	2	1.5	2	1.5	6	4.3	2	1.5	12	2.2
Ocular/visual	0	0.0	1	0.8	0	0.0	0	0.0	1	0.2
Constitutional symptoms	23	16.9	12	9.2	19	13.5	12	9.2	66	12.3
Allergy/immunology	0	0.0	0	0.0	1	0.7	0	0.0	1	0.2
Musculoskeletal/soft tissue	2	1.5	0	0.0	1	0.7	3	2.3	6	1.1
Neurology	6	4.4	10	7.6	4	2.8	3	2.3	23	4.3
Lymphatics	2	1.5	0	0.0	0	0.0	0	0.0	2	0.4
Renal/genitourinary	2	1.5	8	6.1	2	1.4	4	3.1	16	3.0
Dermatology/skin	2	1.5	0	0.0	1	0.7	0	0.0	3	0.6
Vascular	2	1.5	4	3.1	2	1.4	2	1.5	10	1.9
Infection	27	19.9	29	22.1	35	24.8	23	17.7	114	21.2
Metabolic/laboratory	3	2.2	8	6.1	1	0.7	11	8.5	23	4.3
Blood/bone marrow	18	13.2	20	15.3	26	18.4	23	17.7	87	16.2
Cardiac general	1	0.7	1	0.8	2	1.4	2	1.5	6	1.1
Death	0	0.0	0	0.0	1	0.7	1	0.8	2	0.4
Cardiac arrhythmia	3	2.2	2	1.5	3	2.1	2	1.5	10	1.9
Gastrointestinal	28	20.6	19	14.5	25	17.7	29	22.3	101	18.8
Missing	6	–	2	–	1	–	1	–	10	–
Total	136	100	131	100	141	100	130	100	538	100

TABLE 55 Symptoms of non-fatal/life-threatening suspected unexpected serious adverse reactions

Category as defined in *Common Terminology Criteria for Adverse Events, version 3*[54]	Docetaxel (*N* = 2)		Docetaxel + ZA (*N* = 1)		Docetaxel + Sr-89 (*N* = 6)		Docetaxel + ZA + Sr-89 (*N* = 1)		Overall (*N* = 10)	
	n	%	*n*	%	*n*	%	*n*	%	*n*	%
Ocular/visual	0	0.0	0	0.0	1	16.7	0	0.0	1	10.0
Coagulation	0	0.0	0	0.0	1	16.7	0	0.0	1	10.0
Neurology	0	0.0	0	0.0	1	16.7	0	0.0	1	10.0
Dermatology/skin	0	0.0	1	100.0	0	0.0	0	0.0	1	10.0
Vascular	0	0.0	0	0.0	1	16.7	0	0.0	1	10.0
Infection	1	50.0	0	0.0	1	16.7	0	0.0	2	20.0
Cardiac arrhythmia	0	0.0	0	0.0	1	16.7	1	100.0	2	20.0
Gastrointestinal	1	50.0	0	0.0	0	0.0	0	0.0	1	10.0
Total	2	100	1	100	6	100	1	100	10	100

TABLE 56 Symptoms of fatal/life-threatening suspected unexpected serious adverse reactions

Category as defined in *Common Terminology Criteria for Adverse Events, version 3*[54]	Docetaxel (*N* = 7)		Docetaxel + ZA (*N* = 8)		Docetaxel + Sr-89 (*N* = 6)		Docetaxel + ZA + Sr-89 (*N* = 21)		Overall (*N* = 42)	
	n	%	*n*	%	*n*	%	*n*	%	*n*	%
Pulmonary/upper respiratory	3	42.9	2	25.0	1	16.7	2	10.0	8	19.5
Pain	0	0.0	1	12.5	0	0.0	1	5.0	2	4.9
Haemorrhage/bleeding	1	14.3	0	0.0	0	0.0	1	5.0	2	4.9
Constitutional symptoms	0	0.0	1	12.5	0	0.0	0	0.0	1	2.4
Neurology	0	0.0	0	0.0	0	0.0	1	5.0	1	2.4
Hepatobiliary/pancreas	0	0.0	0	0.0	1	16.7	0	0.0	1	2.4
Renal/genitourinary	0	0.0	1	12.5	1	16.7	2	10.0	4	9.8
Vascular	1	14.3	0	0.0	1	16.7	1	5.0	3	7.3
Infection	1	14.3	3	37.5	1	16.7	4	20.0	9	22.0
Blood/bone marrow	0	0.0	0	0.0	0	0.0	3	15.0	3	7.3
Cardiac general	1	14.3	0	0.0	0	0	3	15.0	4	9.8
Death	0	0.0	0	0.0	1	16.7	0	0.0	1	2.4
Gastrointestinal	0	0.0	0	0.0	0	0.0	2	10.0	2	4.9
Missing	0	–	0	–	0	–	1	–	1	–
Total	7	100	8	100	6	100	20	100	41	100

Chapter 4 Economic evaluation

Parts of this chapter are based on the study by Andronis *et al.*[55]

There is considerable uncertainty whether or not the addition of ZA and/or Sr-89 to standard chemotherapy for advanced CRPC patients would represent a cost-effective use of resources. In particular, it is unclear whether or not the extra cost of treatments seeking to alleviate bone-related problems would be balanced out by reduced use of resources – for example, because of a possible reduction in SREs – and improved outcomes. As such, an economic analysis was undertaken on the basis of patient-level data collected alongside the factorial TRAPEZE trial, to assess the cost-effectiveness of two relevant comparisons:

1. ZA versus no ZA
2. Sr-89 versus no Sr-89.

The results of these analyses are expressed in terms of additional cost per QALY gained. The comparison was conducted on the basis of findings suggesting no significant interactions between ZA and Sr-89 in terms of costs (p-value = 0.12) or QALYs (p-value = 0.2). The economic evaluation was based on 707 patients (93% of the total number of 757 patients) for whom the calculation of QALYs was possible, as detailed previously. Two separate analyses are reported for the comparison between ZA and no ZA; the first analysis considers ZA as a branded pharmaceutical, while the second analysis reflects the availability of ZA as a generic product. The ZA patent in the EU expired in May 2013 after completion of the trial.

As this exploration aims to inform clinical practice and resource allocation decisions within the NHS, the methods followed are in agreement with recent recommendations for conducting health technology appraisals.[46] On this basis, the analyses were undertaken from the perspective of the NHS and Personal Social Services, while costs and outcomes occurring in the future were discounted at a rate of 3.5%. Monetary values throughout the study are expressed in UK pounds sterling in 2011–12 prices, when ZA was available only as a proprietary medication. We have recalculated the impact of generic pricing available since May 2013 as a further analysis.

Methods

This section describes the methods followed in estimating the mean per-patient costs and QALYs and the ICERs for the compared options.

Resource use and cost

NHS resource use was captured through CRFs and patient-completed questionnaires and falls into three overarching categories:

1. trial treatment
2. use of related concomitant treatments
3. use of hospital and primary care services.

Trial treatments comprised combinations of docetaxel and prednisolone with (1) ZA (docetaxel, prednisolone and ZA), (2) Sr-89 (docetaxel, prednisolone and Sr-89) or (3) ZA and Sr-89 (docetaxel, prednisolone, ZA and Sr-89). Data on trial treatments provided were obtained from CRFs completed by research nurses. Information on use of treatments or care provided concomitantly with the trial treatments was also obtained from CRFs. Data on duration of inpatient stay and number of outpatient visits were obtained from CRFs for care that were completed during the treatment period, and from patient questionnaires for services provided after the treatment period.

Trial treatment acquisition and administration

The acquisition cost of trial treatments (docetaxel, prednisolone, ZA and Sr-89) was calculated by multiplying patient-specific doses and numbers of cycles received by published unit cost estimates obtained from the *British National Formulary* (BNF).[56] An alternative unit cost estimate was used to reflect the lower acquisition price for ZA owing to the drug being available as a generic product (*Table 57*). With regards to docetaxel, patients received different doses according to their body surface area, which resulted in the use of vials of different volumes. For example, a patient who was administered a dose of docetaxel between 80 mg and 100 mg would require one 4-ml vial and one 1-ml vial at a total cost of £663, whereas a patient administered a dose between 100 mg and 140 mg would require one 7-ml vial at a cost of £720 (see *Table 57*). Prednisolone at a dose of 10 mg per day was given orally together with docetaxel. The daily cost of prednisolone was calculated at £0.64 (approximately £13.50 per 21-day treatment cycle). ZA was provided in doses of up to 4 mg per cycle at a cost of £174 for the branded product or £58 for the generic alternative in additional analyses. Finally, Sr-89 was given as a single fraction of 150 MBq. As the cost of Sr-89 is not available from the BNF, a value was obtained from the Nuclear Medicine Department of the University Hospital Birmingham, Birmingham, UK. This value was varied in sensitivity analyses.

The cost of a chemotherapy administration was taken from the *National Schedule of Reference Costs 2011–12*,[15] with the exception of Sr-89 administrations, the cost of which was obtained from the Nuclear Medicine Department of the University Hospital Birmingham, Birmingham, UK (*Table 58*).

TABLE 57 Constituent parts and unit costs of protocol treatments

Drugs	Dose	Constituent parts	Cost (£)	Source
Docetaxel	1–20 mg	One 1-ml (20-mg) vial	155	BNF[54]
	21–40 mg	Two 1-ml (40-mg) vials	309	BNF[54]
	41–80 mg	One 4-ml (80-mg) vial	508	BNF[54]
	81–100 mg	One 4-ml (80-mg) vial and one 1-ml (20-mg) vial	663	BNF[54]
	101–140 mg	One 7-ml (140-mg) vial	720	BNF[54]
	141–160 mg	One 16-ml (160-mg) vial[a]	1070	BNF[54]
	161–180 mg	One 16-ml (160-mg) vial[a] and one 1-ml (20-mg) vial	1224	BNF[54]
Prednisolone	10 mg daily	30-tablet pack of 5 mg	0.64 a day	BNF[54]
ZA (branded product)	Range of doses up to 3.5 mg	One 5-ml (4-mg) vial	174	BNF[54]
ZA (generic alternative)		One 4 mg/100 ml infusion bottle	58	Department of Health's electronic market information tool
Sr-89	150 MBq	N/A	1710	Nuclear Medicine Department, University Hospital Birmingham, Birmingham, UK

N/A, not applicable.
a Docetaxel vials of 16 ml provide 160 mg of the required chemotherapy infusion (10 mg per 1 ml).

TABLE 58 Unit costs of administration of protocol treatments

Administration	Cost (£)	Source
Docetaxel and prednisolone	245	*National Schedule of Reference Costs 2011–12*[15]
ZA (stand-alone)	245	*National Schedule of Reference Costs 2011–12*[15]
Sr-89 (stand-alone)	443	Nuclear Medicine Department, University Hospital Birmingham, Birmingham, UK

No administration cost was incurred for prednisolone, as the drug is taken orally. When ZA was administered together with docetaxel, no additional cost on top of the administration cost of docetaxel was incurred. However, when ZA was administered as a stand-alone follow-up treatment, it incurred the cost of an outpatient appointment for chemotherapy administration.

Concomitant treatments

Castration-refractory prostate cancer patients received further care or medications provided concomitantly with their trial treatment. Examples include radiotherapy, abiraterone, cabazitaxel, mitoxantrone, blood transfusions, as well as docetaxel, Sr-89 and ZA. The cost of each of these treatments was obtained by multiplying their use, obtained from CRFs, by unit cost estimates available from various sources (*Table 59*). The cost of docetaxel, ZA and Sr-89 given as concomitant medications is the same as in *Table 57*. As information on specific doses for concomitant medications was not available from CRFs, the cost of such medications was calculated on the basis of their recommended dosage as detailed in the BNF.[56]

The cost of administration of concomitant medications given intravenously was obtained from the *National Schedule of Reference Costs 2011–12*[15] and is given in *Table 60*. No administration cost was accounted for abiraterone, which is provided as an oral treatment. The administration cost for docetaxel, Sr-89 and ZA given as second-line treatments is the same as the cost of administration shown in *Table 58*.

Patients who experienced SREs, such as SCC and fractures, would typically receive surgery and/or radiotherapy. Each of the undertaken surgical procedures was matched with a Healthcare Resources Group code and was assigned a cost using the NHS reference cost schedules[15] (*Table 61*). It was assumed that these services were provided on a non-elective basis. Typically, a course of radiotherapy would be on consecutive days and would include a single planning session. Where the gap between fractions was more than 2 weeks, it was assumed that this represented treatment to a different site and a further planning session was added to the model for this separate course of treatment. On this basis, the cost of a radiotherapy session consisted of the cost of the planning visit and the cost of the radiotherapy fraction itself.

TABLE 59 Unit costs of additional concomitant treatments

Drugs	Unit cost	Source
Radiotherapy	£813 cost of radiotherapy preparation plus £118 cost of radiotherapy fraction	*National Schedule of Reference Costs 2011–12*[15]
Abiraterone	£98 per day	BNF[54]
Cabazitaxel	£3696 per cycle	BNF[54]
Mitoxantrone	£100 per cycle	BNF[54]
Blood	£123 per unit plus intravenous cannula (£1) and blood-giving set (£4)	NHS Blood and Transplant[57]

TABLE 60 Unit costs of administration of concomitant treatments

Administration	Unit cost (£)	Source
Cabazitaxel	144	*National Schedule of Reference Costs 2011–12*[15]
Mitoxantrone	245	*National Schedule of Reference Costs 2011–12*[15]
Blood transfusion	172	*National Schedule of Reference Costs 2011–12*[15]

TABLE 61 Unit cost of surgical procedures carried out to address skeletal-related problems

Intervention	Unit cost (£)	Source
Decompression for SCC	9573	*National Schedule of Reference Costs 2011–12*[15]
Laminectomy	6893	*National Schedule of Reference Costs 2011–12*[15]
Intramedullary nailing	4995	*National Schedule of Reference Costs 2011–12*[15]
Hip replacement	8038	*National Schedule of Reference Costs 2011–12*[15]
Pathological fractures with complications	3888	*National Schedule of Reference Costs 2011–12*[15]
SCC	7816	*National Schedule of Reference Costs 2011–12*[15]

As NHS reference cost estimates for surgeries include the cost of an average length of inpatient stay, to avoid double-counting of inpatient stay, the average length of stay specific to each surgery was deducted from the total length of inpatient stay recorded for the patient. The cost of inpatient stay was calculated separately, as described in the next section.

Use of hospital and primary care services

Outpatient appointments, inpatient stays and GP visits which took place during the trial treatment period were obtained from CRFs, while post-treatment stays and visits were obtained from patient-completed questionnaires.

The former were filled in by health-care professionals and were complete for 707 patients, 100% of the available sample for the economic evaluation, whereas the latter presented missing data for 126 patients (approximately 18% of the sample). Multiple imputation by chained equations was used to impute the missing observations.[58] The imputation model made use of predictive mean matching to ensure that the imputed values were consistent with the range of observed values in the trial.[59] Predictor variables used in the model included patient characteristics (age, survival after randomisation, treatment arm allocation), resource use (number of cycles of trial treatment received, use of concomitant medications, number of radiotherapy sessions received, surgeries), as well observed (non-missing) data on outpatient appointments, inpatient stay and GP visits. Unit costs for outpatient appointments, inpatient stay and GP visits were obtained from the NHS reference cost schedules and the Personal Social Services Research Unit's *Unit Cost of Health and Social Care 2012* report[60] (*Table 62*).

TABLE 62 Unit costs of outpatient appointments, inpatient stay and general practice appointments

Service	Unit cost (£)	Source
Inpatient stay	680	*National Schedule of Reference Costs 2011–12*[15]
Outpatient appointment	139	PSSRU's *Unit Cost of Health and Social Care 2012* report[60]
GP consultation	63	PSSRU's *Unit Cost of Health and Social Care* 2012 report[60]

Health-related quality of life and quality-adjusted life-years

A QALY score was derived for each patient on the basis of his responses to the three-level EQ-5D instrument, a generic preference-based measure commonly used in valuing HRQoL. Responses to the instrument's health status classification system were translated into a single preference-based (utility) score using a UK-specific value set.[61] QALYs were calculated as the area under the curve connecting utility scores reported at different time points from baseline to death, at which point utility was assigned a value of zero.[62] Details on the analysis of QoL data and the calculation of QALYs are given in *Chapter 3*, *Quality of life*. For missing questionnaires, no multiple imputation was conducted. The reason for this was that observed responses at time *t* could not be used as predictors of missing responses at time *t* as they corresponded to different time points in patients' treatment and follow-up trajectory.

Analysis

A total NHS cost and a total number of QALYs were calculated for each of the 707 patients for whom information on costs and preference-based QoL (EQ-5D) was available. The base-case analysis, in which the unit cost of ZA was obtained from the BNF, was supplemented by an additional analysis reflecting the availability of generic ZA at a considerably lower price than the proprietary product. The mean total cost and mean total QALYs across all patients under a given treatment were then calculated. As the distribution of costs and QALYs are typically skewed, 95% CIs around mean values were obtained on the basis of 1000 replications using the bias-corrected and accelerated (BCa) bootstrap method.

Incremental analysis was carried out to determine the difference in mean total costs and QALYs between the compared options. These differences were summarised in the form of an ICER, a measure that reflects the extra cost associated with a gain of one additional QALY.[43] To account for the inherent uncertainty in the results because of sampling variation, non-parametric bootstrapping was used to replicate the joint distribution of the differences in cost and QALYs.[63] This generated 5000 paired estimates of incremental costs and QALYs, which were subsequently represented graphically on a cost-effectiveness plane and plotted on CEACs.[47,48] Cost-effectiveness planes show the bootstrap estimates on a four-quadrant plane. Depending on the quadrant in which cost-effectiveness results are located, a treatment may be more effective and more costly (north-east quadrant), more effective and less costly (south-east quadrant), less effective and less costly (south-west quadrant) or less effective and more costly (north-west quadrant) than an alternative treatment. CEACs show the probability of each option being cost-effective across a range of possible values of willingness to pay for an additional QALY. Data management tasks were undertaken in Microsoft Excel 2010 (Microsoft Corporation, Redmond, WA, USA) and statistical analyses, including multiple imputation for missing values, were carried out in Stata version 12.

The impact of different assumptions employed in the cost-effectiveness analysis was assessed in a series of sensitivity analyses. In line with recommendations, and to avoid biased estimates of QALY scores, the analysis controlled for any possible between-group imbalance in baseline EQ-5D QoL scores, using multivariate ordinary least squares regression.[64] Additional sensitivity analyses explored the impact of different plausible values of uncertain parameters in the results, including alternative unit costs for Sr-89, docetaxel and mitoxantrone. As per NICE recommendations, discount rates were varied to no discounting and discounting at 6% for both costs and benefits.[46]

Results of comparison between zoledronic acid and no zoledronic acid

The following section reports the results of the comparison between the ZA and no ZA options in terms of resource use and costs, QALYs and ICERs. Two analyses are reported; the first is based on ZA being a branded product, while the second takes into account the availability of ZA as a generic alternative.

Resource use and cost

The number and proportion of patients that received a trial treatment, concomitant treatment and inpatient, outpatient and primary care services are given in *Chapter 3* and *Appendix 6*. The mean cost for main resource use items are given in *Table 63*.

As expected, the most substantial difference in costs between the ZA and no ZA groups was as a result of the use of ZA (as protocol and follow-up treatment) in the ZA arm. The mean difference in cost between groups associated with the use of ZA was £2197 (BCa 95% CIs £1971 to £2422). With the exception of ZA, patients in the ZA arm presented lower resource use and costs compared with those in the no ZA arm. In particular, there were significant differences in the use of radiotherapies and surgeries. As such care is provided in response to SREs, the lower use and cost of radiotherapy and surgeries is representative of the fact that people in the ZA arm experienced significantly fewer skeletal-related problems.

TABLE 63 Mean per-patient cost for different cost items by treatment group

	ZA ($n = 350$)		No ZA ($n = 357$)		Difference (ZA vs. no ZA)		
	Mean (£)	SD (£)	Mean (£)	SD (£)	Cost difference (£)	Lower CI (£)	Upper CI (£)
Trial treatments							
Docetaxel + prednisolone	2502	760	2441	749	60	–49	169
ZA	1044	456	0	0	1044	1091	996
Sr-89	769	1033	724	1018	45	–107	197
ZA as follow-up treatment	1157	1886	4	67	1153	955	1351
Concomitant medications and treatments							
Radiotherapy	764	1093	1021	1264	–257	–429	–85
Abiraterone	1811	4198	2150	4478	–339	–993	316
ZA as concomitant medication	326	1109	141	681	185	45	324
Sr-89 as concomitant medication	98	476	132	539	–34	–109	41
Blood units	23	150	19	125	4	–16	24
Cabazitaxel	301	1710	293	2230	8	–288	304
Docetaxel as concomitant medication	372	1543	433	2049	–61	–338	216
Mitoxantrone	51	245	26	179	25	–6	56
Surgery	116	988	377	1974	–261	–495	–27
Outpatient appointments and inpatient stay							
Hospital outpatient appointment	672	1015	591	804	81	–51	213
Hospital inpatient stay	3494	6216	3786	6562	–292	–1217	632
GP appointments	278	319	319	384	–42	–95	12

Source: reproduced and amended with permission from Andronis *et al.*[55]

Patients in the ZA arm also showed lower, although not significantly different, costs because of abiraterone, Sr-89 and docetaxel as concomitant medication and lower costs as a result of fewer hospital stays and GP appointments. On the other hand, ZA was associated with higher, although non-significantly different, costs for docetaxel and prednisolone – because of patients in ZA receiving on average more cycles of docetaxel, prednisolone – Sr-89 as trial treatment, blood units, cabazitaxel, mitoxantrone and hospital outpatient appointments.

The estimated mean total cost per patient was £13,776 (BCa 95% CIs £12,824 to £14,728) for ZA and £12,457 (BCa 95% CIs £11,465 to £13,449) for no ZA. This resulted in a mean cost difference of £1319 (BCa 95% CIs –£34 to £2671) (*Table 64*).

The distribution of the total cost can be seen in the box plot in *Figure 39* and histogram in *Figure 40*.

TABLE 64 Mean total per-patient cost for ZA and no ZA

Treatment	Mean (£)	SD (£)	BCa 95% CIs (£)		Difference in cost (ZA vs. no ZA) (£)	BCa 95% CIs of difference (£)	
			Lower CI	Upper CI		Lower CI	Upper CI
ZA	13,776	9118	12,824	14,728	1319	–34	2671
No ZA	12,457	9453	11,465	13,449			

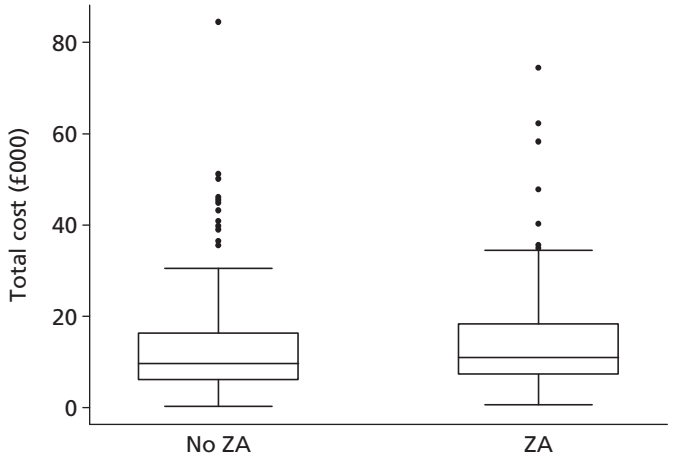


FIGURE 39 Box plot summarising the distribution of total per-patient cost for ZA and no ZA.

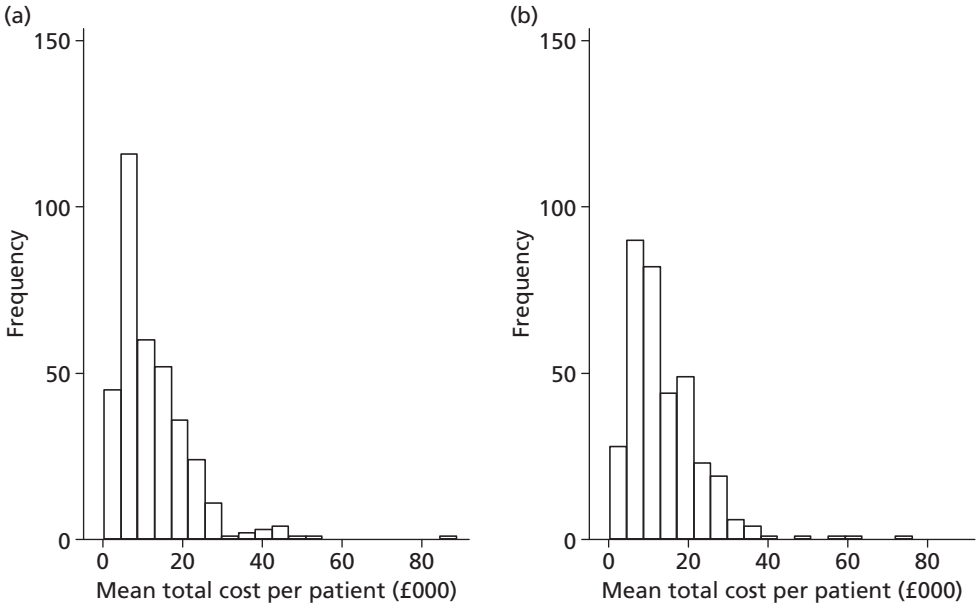


FIGURE 40 Histogram depicting the distribution of the mean total cost for the ZA and no ZA arms. (a) no ZA; and (b) ZA.

Quality-adjusted life-years

Figure 41 depicts the mean EQ-5D scores across treatment groups at three points in time (date of randomisation, 6 and 12 months after randomisation). Mean EQ-5D scores between randomisation and 6 months after randomisation increased in the no ZA group and decreased in the ZA group. This trend was reversed in the period between 6 and 12 months after randomisation, when the mean QoL score for patients in the ZA group increased, while the equivalent value for the no ZA group decreased. It must be noted that caution is needed in comparing EQ-5D scores across time points, as patients returning a questionnaire at the same point in time after randomisations may be at different stages along their treatment and follow-up trajectories (i.e., at 6 months, some patients were still on treatment while others had completed or discontinued their treatment).

Mean numbers of QALYs gained for each treatment are given in *Table 65*. In total, patients in the ZA group gained an average of 0.91 QALYs, suggesting an improvement of 0.03 QALYs over their counterparts in the no ZA group. The distribution of the discounted QALYs is illustrated in *Figure 42*.

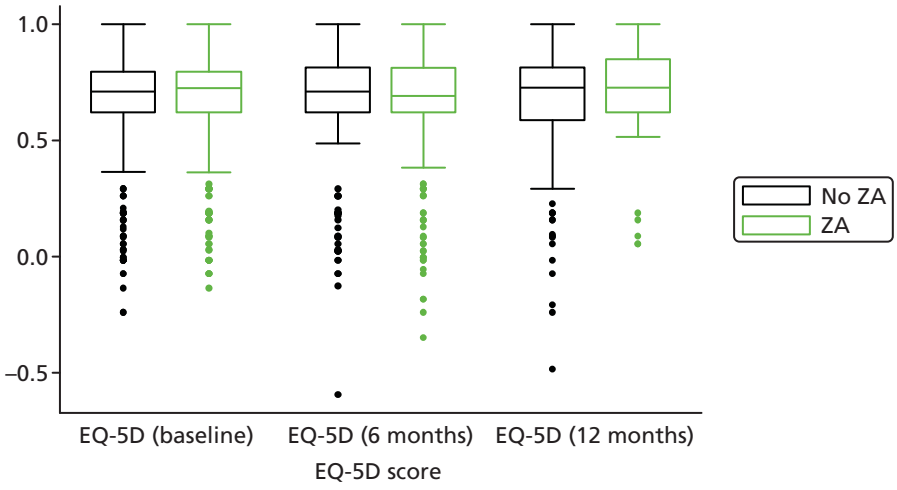


FIGURE 41 Box plot showing the distribution of EQ-5D scores across different time points, for the ZA and no ZA groups.

TABLE 65 Mean per-patient QALYs for ZA and no ZA

	ZA ($n = 350$)		No ZA ($n = 357$)			BCa 95% CI	
	Mean	SD	Mean	SD	Difference	Lower CI	Upper CI
QALYs gained (undiscounted)	0.915	0.697	0.884	0.712	0.031	–0.073	0.134
QALYs gained (discounted)	0.908	0.683	0.876	0.693	0.031	–0.07	0.133

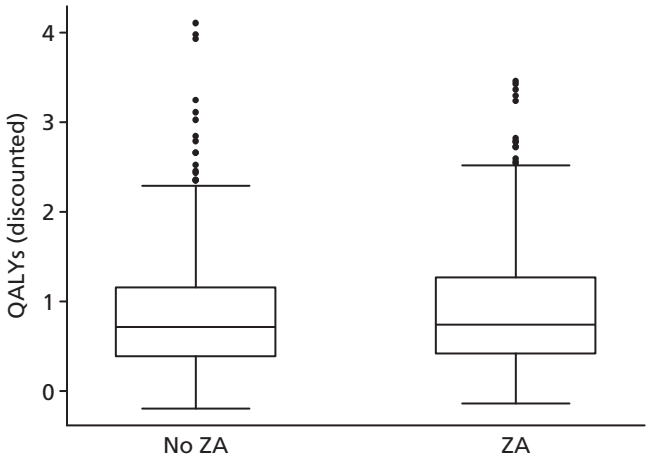


FIGURE 42 Box plot summarising the distribution of discounted QALYs gained for ZA and no ZA.

Cost-effectiveness results

Summary cost and effectiveness results, expressed in terms of a point estimate ICER, are shown in *Table 66*. ZA appeared to be more costly than no ZA, resulting in an estimated incremental cost of £1319. This difference is mainly driven by the additional cost of ZA in the ZA group. In terms of QALYs gained, ZA appeared to be slightly more effective than no ZA, resulting in a gain of 0.03 QALYs. Given the above, the point estimate ICER for ZA compared with no ZA is £42,047 per additional QALY. This value is considerably greater that the ratio of £20,000 to £30,000 per QALY which is perceived to represent a cost-effective use of resources by NICE.[46]

Figure 43 depicts the results of 5000 bootstrap replications plotted on the cost-effectiveness plane. Each point represents a pair of incremental cost and incremental effectiveness estimates for the comparison between ZA and no ZA. Approximately 71% of the simulated pairs are located in the north-east quadrant, indicating that ZA is likely to be more costly and more effective than no ZA. About 26% of the points appear in the north-west quadrant, which indicates that ZA is more costly and less effective than no ZA. There are also a small number of points located in the southern half of the plane, indicating that ZA may be less costly and more effective than no ZA (south-east quadrant; 1% of all points) or less costly and less effective than no ZA (south-west quadrant; 2% of all points).

Figure 44 depicts the CEACs for ZA and no ZA, showing the probability of each of the option being cost-effective at different values of a decision-maker's willingness to pay for a QALY (ceiling ratio). In a situation in which the decision-maker is not prepared to pay any amount for additional health benefits (i.e. the ceiling ratio is zero), the probabilities of ZA and no ZA being cost-effective are 3% and 97%, respectively. At values of the ceiling ratio between £20,000 and £30,000 per QALY, the probability of ZA being cost-effective rises from 26% to 40%; it exceeds 50% (i.e. appears to be the most cost-effective treatment) for ceiling ratios over £42,000 per QALY.

TABLE 66 Point estimate ICER for the comparison between ZA and no ZA

Treatment	Total cost (£)	Total QALYs	Difference in cost (ZA vs. no ZA) (£)	Difference in QALYs (ZA vs. no ZA)	ICER (£)
ZA	£13,776	0.908	1319	0.031	42,047
No ZA	£12,457	0.876			

FIGURE 43 Cost-effectiveness plane showing incremental cost and effect (QALYs) pairs for the comparison between ZA and no ZA.

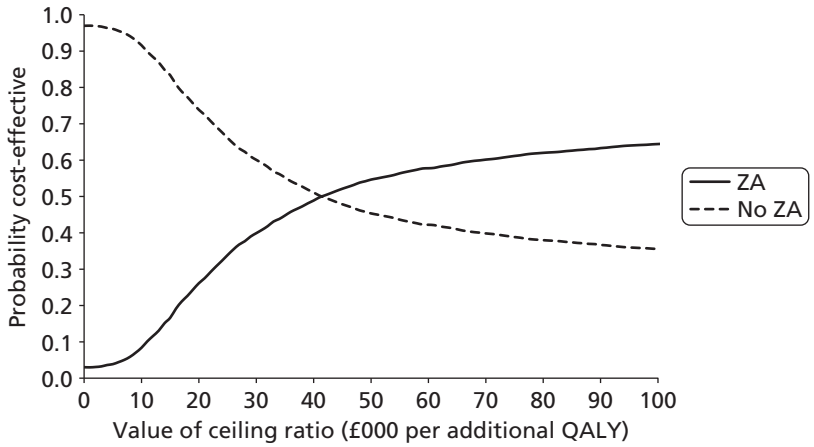


FIGURE 44 Cost-effectiveness acceptability curves showing the probability of ZA and no ZA being cost-effective at different values of the ceiling ratio.

Additional analysis to account for the availability of generic zoledronic acid

Generic alternatives to ZA have now become available and are in use in NHS hospitals, at a significantly lower price than the proprietary alternatives (Zometa®, East Hanover, NJ, USA, or Aclasta®, Surrey, UK). Given this, additional analysis was undertaken to reflect the fact that NHS hospitals are likely to face a lower acquisition cost for ZA.

An estimate of the average price paid by NHS hospitals for ZA in 2013 (£58 per 4 mg/100 ml infusion bottle) was obtained from the electronic market information tool (eMIT) of the Department of Health Commercial Medicines Unit.[65]

The use of this unit cost estimate resulted in a marked decrease in the cost of ZA when given as trial treatment, follow-up treatment and concomitant medication (*Table 67*). As expected, the cost associated with the use of ZA in the ZA group was still higher than the equivalent cost in the no ZA group; nonetheless, the difference between groups is now considerably smaller.

As the cost of ZA itself is a main driver of the total cost of ZA, the use of lower prices for ZA led to a decrease in the total per-patient cost for ZA and, consequently, the difference in total costs between ZA and no ZA was reduced to £251 (BCa 95% CI £–1099 to £1602) (*Table 68*).

The reduced incremental cost combined with the observed change in QALYs gave a point estimate ICER of £8005 per additional QALY (*Table 69*).

TABLE 67 Mean per-patient cost for different cost items on the basis of generic ZA

	ZA ($n = 350$)		No ZA ($n = 357$)		Difference (ZA vs. no ZA)		
Treatment	Mean (£)	SD (£)	Mean (£)	SD (£)	Cost difference (£)	Lower 95% CI (£)	Upper 95% CI (£)
ZA	346	151	0	0	346	330	361
ZA as follow-up treatment	837	1358	3	48	834	692	977
ZA as concomitant medication	235	801	101	492	134	36	230

TABLE 68 Mean total per-patient cost for ZA and no ZA using generic prices for ZA

			BCa 95% CIs (£)		Difference in cost (ZA vs. no ZA) (£)	BCa 95% CIs of difference (£)	
Treatment	Mean (£)	SD (£)	Lower CI	Upper CI		Lower CI	Upper CI
ZA	12,667	8795	11,724	13,612	251	–1099	1602
No ZA	12,417	9433	11,436	13,397			

TABLE 69 Point estimate ICER for the comparison between ZA and no ZA, using generic prices for ZA

Treatment	Total cost (£)	Total QALYs	Difference in cost (ZA vs. no ZA) (£)	Difference in QALYs (ZA vs. no ZA)	ICER (£)
ZA	12,667	0.908	251	0.031	8005
No ZA	12,417	0.876			

Uncertainty around incremental costs and QALYs, propagated through 5000 bootstrap replications, is plotted on the cost-effectiveness plane in *Figure 45*. Approximately half (51%) of the simulated pairs are located in the north-east quadrant, indicating that ZA is likely to be more costly and more effective than no ZA. About 14% of the pairs appear in the north-west quadrant (i.e. ZA is more costly and less effective than no ZA), while 21% of the pairs are located in the south-east quadrant (i.e. ZA is less costly and more effective than no ZA). The remaining 14% of the pairs are located in the south-west quadrant (i.e. ZA is less costly and less effective than no ZA).

Cost-effectiveness acceptability curves showing the probability of ZA and no ZA being cost-effective at different ceiling ratios are depicted in *Figure 46*. In a situation in which the decision-maker is not prepared to pay any amount for additional health benefits (i.e. the ceiling ratio is zero), the probabilities of ZA and no ZA being cost-effective are 35% and 65%, respectively. ZA appears to be the most cost-effective option at ceiling ratios over £8000 per QALY, and at £20,000 and £30,000 per QALY the probability of ZA being cost-effective is 64% and 68%, respectively.

Figure 47 depicts ICER values for ZA as a function of possible prices of ZA. For prices of ZA between £0 and £31, the total per-patient cost of ZA is lower than that of no ZA and, given the fact that ZA is associated with additional QALYs, this treatment option dominates its comparator. For prices between £31 and £98, ZA results in ICERs up to £20,000 per QALY, and it is thus cost-effective at this ceiling ratio. For prices of ZA higher than £98, the resulting ICER exceeds £20,000 per QALY.

FIGURE 45 Cost-effectiveness plane showing incremental cost and effect (QALYs) pairs for the comparison between ZA and no ZA, based on the availability of generic ZA.

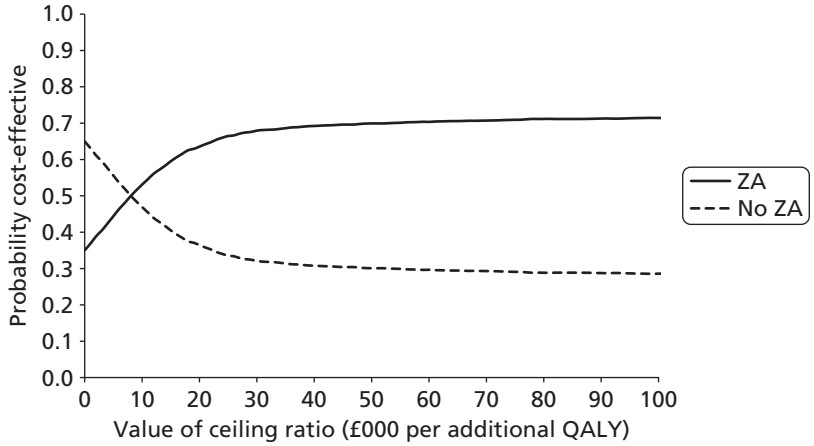


FIGURE 46 Cost-effectiveness acceptability curves showing the probability of generic ZA and no ZA being cost-effective at different values of the ceiling ratio. Reproduced and amended with permission from Andronis *et al.*[55] In the source figure, only the ZA CEAC was plotted; a CEAC for No ZA has been added here.

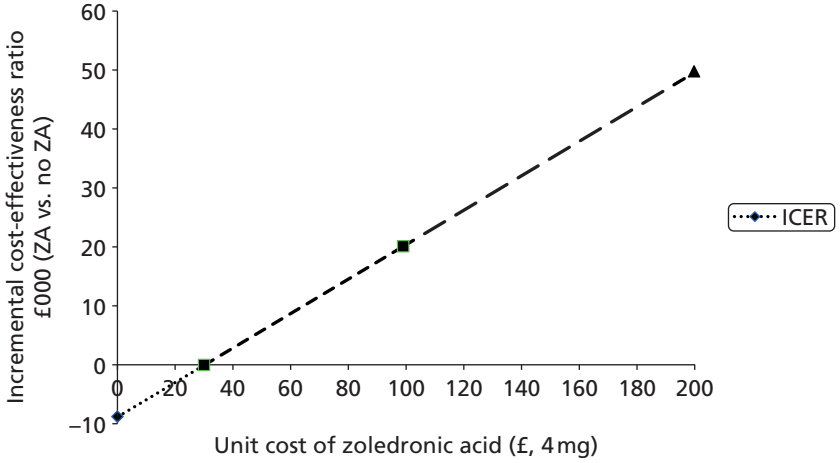


FIGURE 47 Incremental cost-effectiveness ratio for ZA vs. no ZA for different prices of ZA.

Sensitivity analysis

Most of the alternative assumptions explored in sensitivity analyses appeared to have a small effect on the magnitude of cost and benefits and, consequently, a limited impact on the resulting ICER. First, when future costs and benefits were not discounted, there was a small increase in both costs and QALYs, giving a slightly increased ICER value for ZA of £42,500 per additional QALY. On the other hand, discounting at a higher rate of 6% per annum led to a small decrease in the ICER, which, under this scenario, assumed a value of £41,851. Using alternative unit cost estimates for docetaxel and mitoxantrone from the NHS Commercial Medicines Unit[65] had a small effect on the total mean cost per patient, with lower prices of docetaxel and mitoxantrone compared with the base-case values from BNF resulting in ICERs of £43,250 and £41,950, respectively. Sensitivity analyses around the price of Sr-89 had no significant effect on the differences in costs between the ZA and no ZA arms, and gave ICERs close to the £42,000 per QALY mark.

A different pattern was observed when adjusting QALYs for baseline imbalances in EQ-5D scores. Such an adjustment had a significant impact on the difference in QALYs between the compared groups, with no ZA appearing to be slightly more effective than ZA (difference of –0.001 QALYs, 95% CI –0.096 to 0.094). Under this scenario, the ZA group appears to be more expensive and less effective than no ZA, and thus it is extendedly dominated by the latter (*Table 70*).

TABLE 70 Results of sensitivity analysis for ZA and no ZA

	ZA		No ZA		
	Mean cost (£)	Mean QALYs	Mean cost (£)	Mean QALYs	ICER (£)
Base-case results	13,776	0.908	12,457	0.876	42,047
No discounting	13,897	0.915	12,592	0.884	42,449
Discounting at 0.06 per annum for both costs and benefits	13,695	0.903	12,366	0.871	41,851
QALYs adjusted for baseline imbalances in EQ-5D	13,776	0.875	12,457	0.876	ZA dominated
Unit cost of docetaxel from eMIT (£34.29 for 140 mg)	12,618	0.908	11,261	0.876	43,251
Unit cost of mitoxantrone from eMIT (£60.36 for 25 mg)	13,770	0.908	12,454	0.876	41,956
Unit cost of Sr-89 (75% of available estimate)	13,757	0.908	12,431	0.876	42,261
Unit cost of Sr-89 (125% of available estimate)	13,795	0.908	12,483	0.876	41,832

Results of comparison between strontium-89 and no strontium-89

The following section reports the results of the comparison between Sr-89 and no Sr-89 in terms of resource use and costs, QALYs and ICERs.

Resource use and cost

The number and proportion of patients who received a trial treatment, concomitant treatment and inpatient, outpatient and primary care are given in *Appendix 5*. The mean costs for main resource use items are given in *Table 71*.

As expected, the most prominent difference in mean costs between the Sr-89 and no Sr-89 groups is a result of the cost of Sr-89 itself. Apart from higher cost of Sr-89, the Sr-89 group was associated with greater cost for docetaxel and ZA given as protocol treatments, higher cost of cabazitaxel and docetaxel provided as concomitant medications and increased cost as a result of surgeries. On the other hand, the Sr-89 group was associated with lower use of radiotherapies, abiraterone, ZA and Sr-89 as concomitant medications, as well as fewer inpatient days, outpatient appointments and GP visits.

The estimated mean total cost per patient was £13,787 (BCa 95% CI £12,862 to £14,713) for Sr-89 and £12,446 (BCa 95% CI £11,489 to £13,403) for no Sr-89. This resulted in a mean cost difference of £1341 (BCa 95% CI –£66 to £2748) (*Table 72*).

The distribution of the total cost can be seen in the box plot *Figure 48* and histogram *Figure 49*.

TABLE 71 Mean per-patient cost for different cost items by treatment group

	Sr-89 ($n = 350$)		No Sr-89 ($n = 357$)		Difference (Sr-89 vs. no Sr-89)		
	Mean (£)	SD (£)	Mean (£)	SD (£)	Cost difference (£)	Lower 95% CI (£)	Upper 95% CI (£)
Trial treatments							
Docetaxel + prednisolone	2497	738	2445	771	52	–61	165
ZA	525	613	508	613	18	–71	107
Sr-89	1507	988	0	0	1507	1407	1608
ZA as follow-up treatment	539	1337	609	1549	–69	–279	141
Concomitant medications							
Radiotherapy	803	1033	983	1318	–180	–349	–11
Abiraterone	1905	4279	2058	4408	–153	–814	508
ZA as concomitant medication	205	866	259	975	–54	–192	84
Sr-89 as concomitant medication	110	527	120	492	–9	–85	66
Blood units	21	150	21	124	0	–20	21
Cabazitaxel	375	2192	221	1765	154	–134	443
Docetaxel as concomitant medication	415	2057	390	1545	25	–233	283
Mitoxantrone	39	218	39	211	0	–32	31
Surgery	325	1954	172	1064	153	–84	390
Outpatient appointments and inpatient stay							
Hospital outpatient appointment	609	889	653	940	–44	–178	89
Hospital inpatient stay	3630	6294	3653	6491	–23	–950	903
GP appointments	281	350	316	357	–35	–86	16

Source: reproduced and amended with permission from Andronis *et al.*[55]

TABLE 72 Mean total per-patient cost for Sr-89 and no Sr-89

			Bootstrapped 95% CIs			Bootstrapped 95% CIs of difference	
Treatment	Mean	SD	Lower CI	Upper CI	Difference	Lower CI	Upper CI
Sr-89	£13,787	£9295	£12,862	£14,713	£1341	–£66	£2748
No Sr-89	£12,446	£9281	£11,489	£13,403			

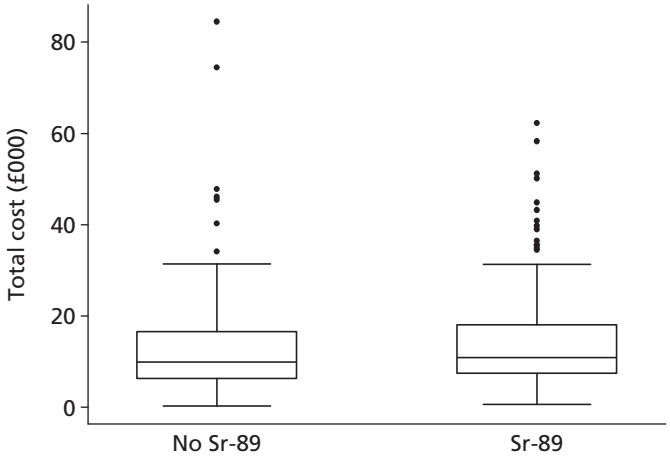


FIGURE 48 Box plot summarising the distribution of total per-patient cost for Sr-89 and no Sr-89.

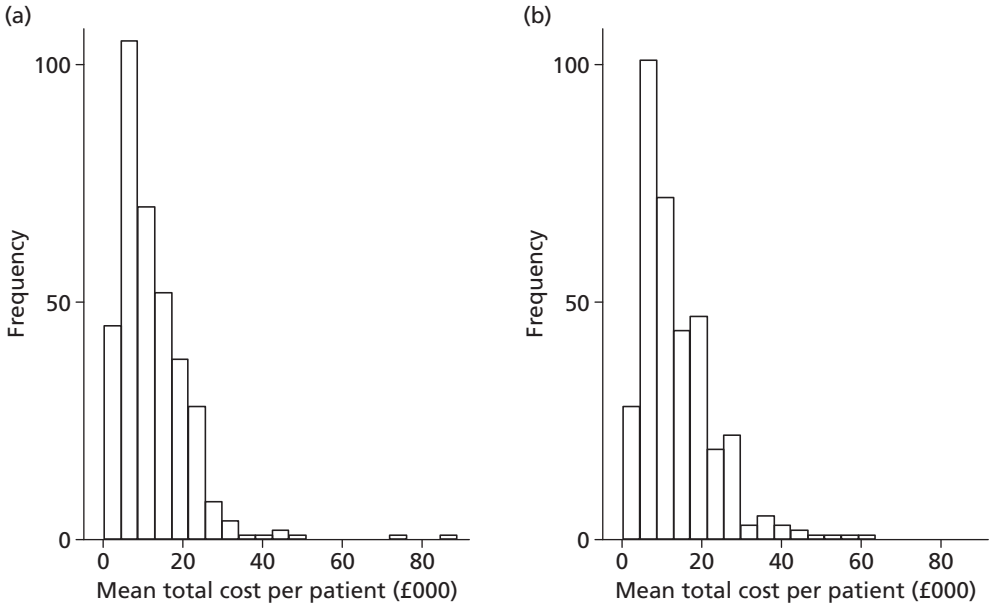


FIGURE 49 Histogram depicting the distribution of the mean total cost for the Sr-89 and no Sr-89 groups. (a) No Sr-89; and (b) Sr-89.

Quality-adjusted life-years

Figure 50 shows the distribution of EQ-5D scores at baseline and at 6 and 12 months after randomisation for the Sr-89 and no Sr-89 groups. Throughout the first year after randomisation, both groups presented approximately the same average increase in QoL. Again, it must be noted that, while responses relate to a specific point in time (e.g. 6 months), patients at this point in time may be at different stages of their treatment and follow-up pathways.

The mean and standard deviation of the distribution of discounted and undiscounted QALYs for each treatment are given in *Table 73*. These distributions are depicted as box plots in *Figure 51*.

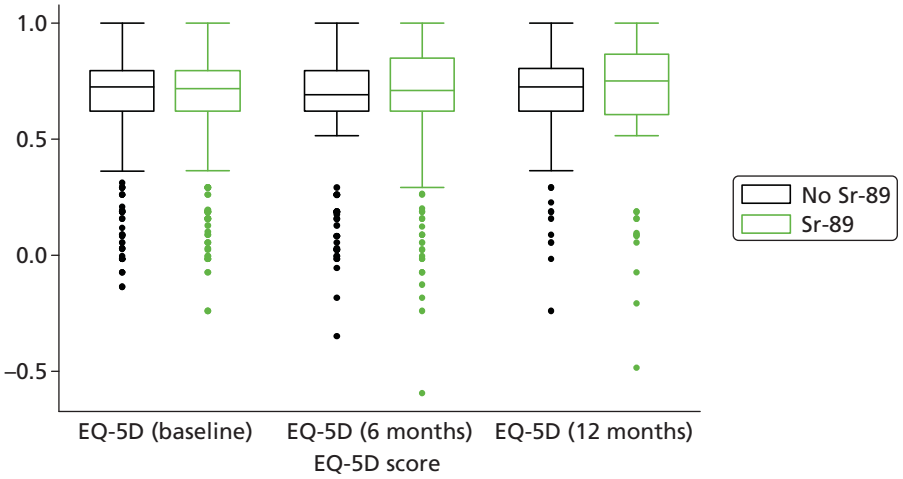


FIGURE 50 Box plot showing the distribution of EQ-5D scores across different time points, for the Sr-89 and no Sr-89 groups.

TABLE 73 Quality-adjusted life-years for Sr-89 and no Sr-89

	Sr-89 ($n = 350$)		No Sr-89 ($n = 357$)			BCa 95% CI	
	Mean	SD	Mean	SD	Difference	Lower CI	Upper CI
QALYs (undiscounted)	0.941	0.741	0.859	0.665	0.082	–0.021	0.184
QALYs (discounted)	0.933	0.725	0.852	0.648	0.081	–0.019	0.181

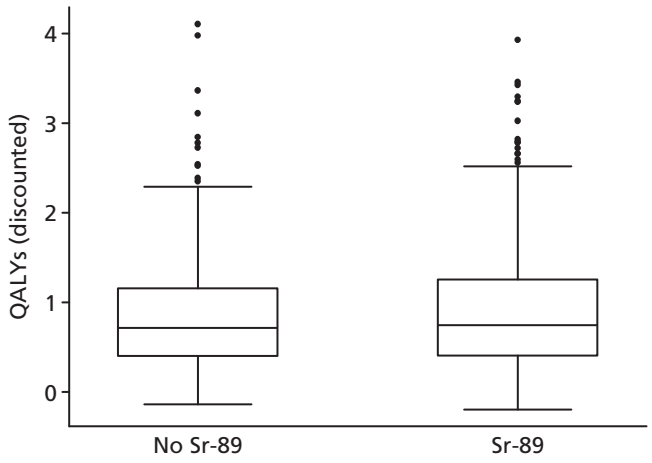


FIGURE 51 Box plot summarising the distribution of QALYs for Sr-89 and no Sr-89.

Cost-effectiveness results

Differences in mean total per-patient cost and mean overall QALYs between the Sr-89 and no Sr-89 groups can be seen in *Table 74*. Sr-89 appears to be more costly than no Sr-89, resulting in a between-group difference of approximately £1350. In terms of QALYs, Sr-89 is slightly more effective, indicating a gain of 0.08 QALYs over no Sr-89. Given these differences in costs and QALYs, the point estimate ICER for Sr-89 compared with no Sr-89 was calculated at £16,590 per additional QALY. This value is well below the £20,000 per QALY ratio which NICE considers to represent effective use of the NHS resources.[46]

Pairs of differences in costs and QALYs between the two groups, generated through 5000 bootstrap replications, are depicted on the cost-effectiveness plane (*Figure 52*). Approximately 91% of the simulated pairs are located in the north-east quadrant, pointing to a substantial likelihood that Sr-89 is more costly and at the same time more effective than no Sr-89. About 6% of the points appear in the north-west quadrant, which indicates that Sr-89 may be more costly and less effective than no Sr-89. The rest of the points – approximately 3% of the 5000 estimates – fall in the southern half of the plane, indicating that Sr-89 may be less costly and more effective than no Sr-89 (south-east quadrant; 2% of all points) or less costly and less effective than no Sr-89 (south-west quadrant; 1% of all points).

The CEAC for Sr-89 and no Sr-89 is given in *Figure 53*. In the situation that the decision-maker is not prepared to pay any amount for additional QALYs – that is, the ceiling ratio is zero – the likelihoods of Sr-89 and no Sr-89 being cost-effective are 97% and 3%, respectively. As the value of the ceiling ratio rises, the

TABLE 74 Point estimate ICER for the comparison between Sr-89 and no Sr-89

Treatment	Total cost (£)	Total QALYs	Difference in costs (£) (Sr-89 vs. no Sr-89)	Difference in QALYs (Sr-89 vs. no Sr-89)	ICER (£)
Sr-89	13,787	0.933	1341	0.081	16,590
No Sr-89	12,446	0.852			

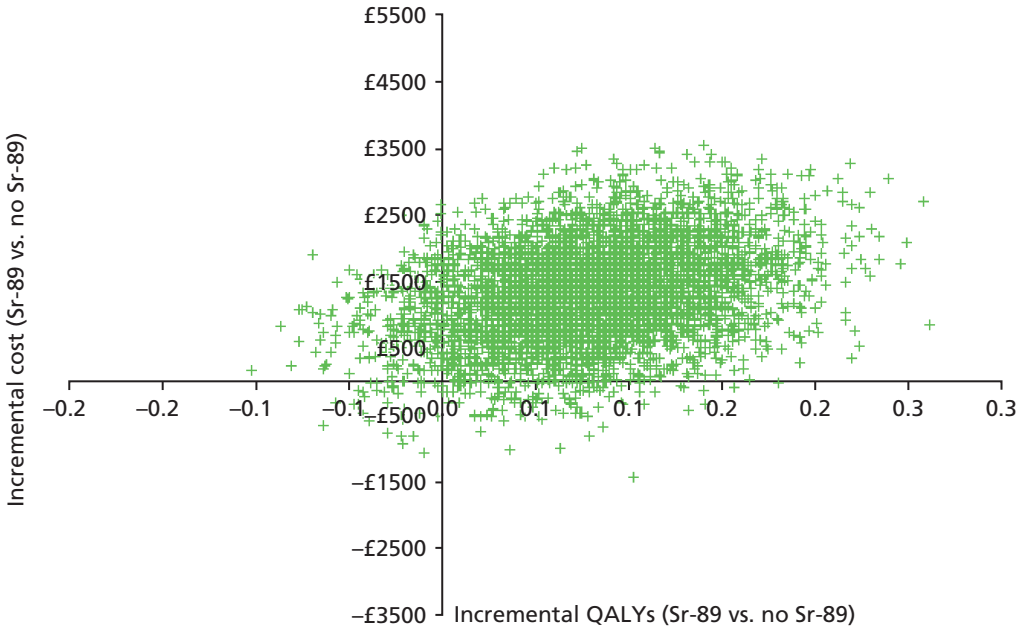


FIGURE 52 Cost-effectiveness plane showing incremental cost and effect (QALYs) pairs for the comparison between Sr-89 and no Sr-89.

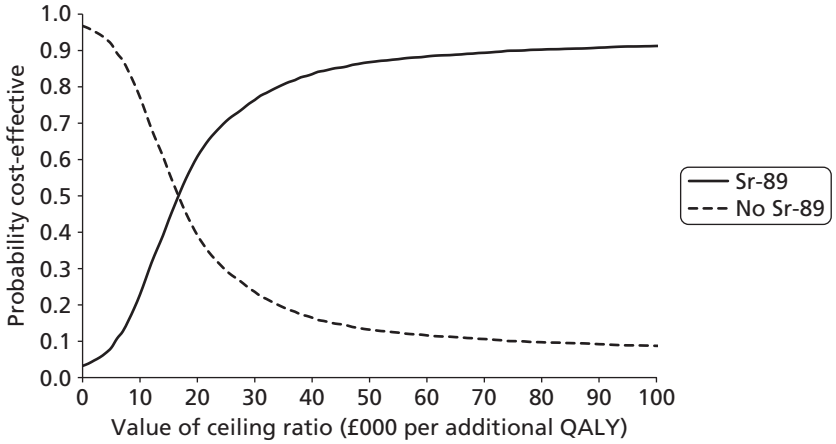


FIGURE 53 Cost-effectiveness acceptability curve showing the probability of Sr-89 and no Sr-89 being cost-effective at different values of the ceiling ratio. Reproduced and amended with permission from Andronis *et al.*[55] In the source figure, only the Sr-89 CEAC was plotted; a CEAC for No Sr-89 has been added here.

likelihood of Sr-89 being the most cost-effective option increases steadily and reaches 50% at about £16,600 per QALY. For ceiling ratios between £20,000 and £30,000 per QALY gained, the probability that Sr-89 is more cost-effective than no Sr-89 ranges from 61% to 76%. If society is willing to pay more than £20,000 for an additional QALY, the chance that Sr-89 is the most cost-effective option is in excess of 61%.

Sensitivity analysis

Different scenarios were explored in the sensitivity analysis and are presented in *Table 75*. Most scenarios appeared to have a limited impact on the resulting ICER. In particular, not discounting costs and QALYs and discounting costs and benefits at 0.06% per year resulted in ICERs for Sr-89 of £16,520 and £16,650 per QALY, respectively. After adjusting for baseline utility, the calculated QALYs for the Sr-89 group remained greater than the QALYs of the no Sr-89 group (difference of 0.073 QALYs, 95% CI –0.019 to 0.166). This resulted in an ICER of £18,325. Using alternative unit cost estimates for docetaxel and mitoxantrone

TABLE 75 Results of sensitivity analysis for Sr-89 and no Sr-89

	Sr-89		No Sr-89		
	Mean cost	Mean QALYs	Mean cost (£)	Mean QALYs	ICER (£)
Base-case results	13,787	0.933	12,446	0.852	16,590
No discounting	13,920	0.941	12,570	0.859	16,517
Discounting at 0.6 per annum for both costs and benefits	13,698	0.927	12,363	0.847	16,646
QALYs adjusted for baseline imbalances in EQ-5D	13,787	0.925	12,446	0.852	18,325
Unit cost of docetaxel from eMIT (£34.29 for 140 mg)	12,592	0.933	11,287	0.852	16,151
Unit cost of mitoxantrone from eMIT (£60.36 for 25 mg)	13,783	0.933	12,442	0.852	16,591
Unit cost of ZA (50% lower than BNF price)	13,371	0.933	12,012	0.852	16,777
Unit cost of ZA (90% lower than BNF price)	13,038	0.933	11,665	0.852	16,952
Unit cost of ZA (£57.71 for 4 mg)	13,230	0.933	11,865	0.852	16,851
Unit cost of Sr-89 (75% of available estimate)	13,488	0.933	12,446	0.852	12,889
Unit cost of Sr-89 (125% of available estimate)	14,086	0.933	12,446	0.852	20,292

from the NHS Commercial Medicines Unit[65] had a minimal effect on the total mean per-patient cost, with prices of docetaxel and mitoxantrone lower than the base-case values from BNF, resulting in ICERs of £16,150 and £16,590 per QALY, respectively. The use of lower acquisition cost for ZA to reflect the availability of generic alternatives had a limited effect on the difference in cost between Sr-89 and no Sr-89 and, thus, it had a minimal impact on the resulting ICER.

As expected, sensitivity analyses around the price of Sr-89 had a more profound effect on the differences in costs between Sr-89 and no Sr-89; a lower price of Sr-89 showed Sr-89 to be associated with an ICER of £12,900 per QALY, whereas a higher price for this radioisotope resulted in an ICER for Sr-89 slightly over £20,000 per QALY. The relationship between the price of Sr-89 and the resulting ICER for Sr-89, as compared with no Sr-89, is depicted in *Figure 54*; it can be seen that for prices of Sr-89 up to £2120, the ICER for ZA is below £20,000 per QALY and, thus, Sr-89 is cost-effective at the ceiling ratio of £20,000 per QALY.

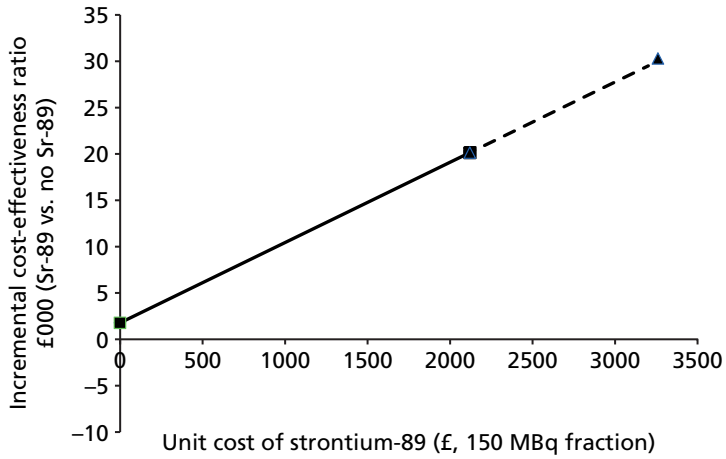


FIGURE 54 Incremental cost-effectiveness ratio for Sr-89 vs. no Sr-89 for different prices of Sr-89.

Chapter 5 Discussion

Interpretation

There are two strands to the discussion: the clinical effectiveness of the two treatments and the health economic aspects. As there was no interaction between the effects of the two therapies, Sr-89 and ZA, the effects can be considered separately.

Strontium-89

The addition of Sr-89 to chemotherapy did favourably affect time to bony disease progression and had a modest effect on QoL, but no effect on OS. Surprisingly, given the previous data for Sr-89, there was no impact on SREs in terms of time to first SRE, total numbers or distribution. Given the lack of impact on events such as SREs, there was little impact on downstream costs. However, the observed QoL gain and modest additional cost (£1341) translated into an ICER of £16,590 per additional QALY.

Despite these positive outcomes, it is less clear whether or not findings will significantly alter the use of Sr-89, for a number of reasons. First, the gain in CPFS is modest – about 1 month – while, at the same time, there was no impact on SRE frequency or time to first event. At the time of study inception, this gain in CPFS, coupled with a QoL gain, would certainly have been practice-changing at an ICER well below £20,000 per QALY. However, we have seen a number of new treatments licensed in the last few years that improve OS after chemotherapy and bring improvements in QoL and SREs. These include abiraterone,[8] enzalutamide,[9] cabazitaxel[16] and, of particular relevance to this study, radium-223.[18] Radium-223 is a radioisotope with a similar uptake mechanism of action to Sr-89, being a calcium-mimetic agent. However, it is more intensely radioactive and the key ALSYMPCA trial[18] shows improvements in both OS and symptomatic SREs. In addition, the SRE benefit appears to be potentiated by concurrent use of bisphosphonates.

Zoledronic acid

The addition of ZA to docetaxel did not impact on OS or affect CPFS after chemotherapy. There was, however, a substantial impact on symptomatic SREs. As indicated in *Chapter 1*, *Bisphosphonates*, SREs are controversial as they are a composite end point, and in the ZA licensing trials a key component, pathological fracture, was assessed repeatedly by a blinded radiologist. The consequence was that many SREs in the trials were of uncertain clinical significance. In contrast, in TRAPEZE and in some other recent trials in CRPC such as the ALSYMPCA study with radium-223,[18] only symptomatic SREs have been collected; hence the clinical and economic consequences are much clearer. The US Food and Drug Administration now refers to symptomatic SREs as 'symptomatic skeletal events', which is probably a helpful and relevant distinction. We shall continue to use the term SRE in this report, as this is the terminology used throughout the study. In the trial, ZA produced a substantial increase in time to first SRE (13.6 months vs. 11.17 months; HR 0.78), a substantial decrease in SREs (total SREs 605 vs. 424), as well as a decrease in SREs per patient (see *Figure 15*). Furthermore, when the distribution of SREs by type is considered, the biggest effect of ZA was on the SREs that may be considered the most severe (fracture, SCC and surgery to bone), with a near 50% reduction, compared with radiotherapy, which reduced these SREs by about one-third (see *Table 34*).

With this background of clinical effect, the QoL data are of considerable interest. The first feature to note is that QoL is well preserved across the course of the illness. This accords with clinical impression, which is that patients remain well in the majority of cases until the final terminal period. The data collected are undoubtedly incomplete, because the final terminal phase does not seem to be well captured as patients are generally not attending trials clinics in that period. The second feature is that ZA had a positive, albeit minimal, effect on QoL, despite a marked change in distribution of SREs in particular. How may we explain this, as events such as pain leading to radiotherapy, fracture and SCC must certainly impair QoL? There are a number of possibilities. The first relates to the fact that the timing of completion of forms was variable

and hence may well have occurred only in the stable outpatient environment of the trials clinic, once problems were resolved. The second is that, after a serious event such as a fracture, patients cease to attend the trial clinic and so the detriment to QoL from a SRE is not well captured. The third is that as the serious SREs are a minority, any effect is drowned by the QoL impact of radiotherapy, which, it could be postulated, is as good a way of maintaining QoL as regular ZA infusions. In truth it is likely that all of these explanations are partially true.

From an economic viewpoint, our cost-effectiveness analysis showed the ZA group to be associated with an additional cost of £1319 compared with no ZA, on the premise that ZA is purchased as a branded product at the price reported in the BNF. Combined with the small increase in QoL, ZA appeared to be more costly and more effective than no ZA, resulting in an ICER near the £42,000 per QALY mark.

However, since the completion of the TRAPEZE trial, ZA has become available as a generic product at a significantly lower price – less than one-third of the price of the branded Zometa. Indeed, according to the NHS Commercial Medicines Unit, the average price that hospitals across England pay for ZA is one-third of the price of proprietary products listed in BNF. As the cost of adding ZA to chemotherapy is a main driver of the difference in total cost between ZA and no ZA, accounting for this showed lower additional costs associated with ZA (£251) and a markedly lower ICER of £8005 per QALY. In addition, prevention of serious events, such as fracture, surgery and cord compression (all associated with frequent and prolonged admissions), is a high priority for NHS trusts with great pressures on beds. Therefore, a predictable outpatient therapy with modest net acquisition costs may well be attractive to trusts if it prevents emergency, unpredictable visits. We did not carry out a patient preference study; however, it may well be the case that patients would prefer a preventative treatment such as ZA to a reactive approach.

Limitations

The main limitations of the data presented are largely discussed above. Specifically, the development of new treatments for CRPC makes Sr-89 in particular less relevant, with the advent of better radioisotope therapy such as radium-223. The limitations on the ZA data are more complex, as the effects on SREs are substantial and result in reduced costs associated with surgery and radiotherapy at a modest additional cost. It is likely that these benefits are complementary to those achieved with other post-docetaxel therapies. In particular, there are data available showing that the benefit of radium-223 on SREs may be increased by ZA. Improved bone-protecting agents that prevent hospital visits may also alter the potential benefits of these agents.

A further problem with the QoL data is the effect of missing data, which we have attempted to model but which could clearly influence outcomes, as it is likely that we are missing data, in particular relating to QoL around SREs and in the terminal phases. In line with recommendations, health benefits accruing from the compared treatments were measured in terms of QALYs on the basis of patient responses to the EQ-5D (three-level) preference-based QoL instrument. However, it must be noted that, in such terminal phases, benefits perceived to be relevant by patients may not be fully captured by instruments such as the EQ-5D and they may be inadequately reflected on QALYs. As Gomes *et al.*[66] point out, this is largely because, at the end-of-life stage, patients deem improvements in survival and QoL as secondary considerations. Despite this, no instruments are available to measure benefits of end-of-life care for the purposes of economic evaluations. Costs in this paper have been derived from patient-reported resource use data and, thus, may be subject to recall bias.

Generalisablity

Docetaxel remains a mainstay of therapy for CRPC despite the development of new treatments for the disease. Of note is the fact that, although all patients recruited to the study had relapsing bone mCRPC, around 40% of patients died without experiencing a single SRE in the docetaxel arm (fewer with the addition of ZA). Hence, docetaxel itself can be imputed to effectively prevent SREs, as it is highly likely that the majority of patients managed without this agent (in the era prior to the new therapies listed previously) would have had many SREs. The data on QoL are striking for the way that QoL is maintained in a highly disease-burdened population. QoL also rose on commencement of chemotherapy, underlining its value as a palliative treatment.

As noted, Sr-89 has probably been superseded by radium-223, as well as by other treatments of higher effectiveness for CRPC. On the other hand, bone-protecting agents such as ZA may offer complementary benefits via their impact on SREs, particularly serious ones.

Overall evidence

Strontium-89 after six cycles of docetaxel improved CPFS but not OS. ZA did not improve CPFS or OS but did significantly improve median SREFI, mostly after progression, suggesting a role as post-chemotherapy maintenance therapy. QoL was well maintained in all treatment arms but with differing patterns of care resulting from the effects of Sr-89 on time to progression and ZA on SREFI and total SREs.

The addition of Sr-89 to docetaxel chemotherapy resulted in an additional cost of £1341, mainly because of the cost of the Sr-89 acquisition and administration. Combined with a positive, although small, increase in QALYs, this option resulted in an ICER of £16,590 per QALY compared with no use of Sr-89. This value is below the commonly cited willingness-to-pay value of £20,000 per additional QALY.

The addition of ZA to docetaxel resulted in an extra cost of about £1320 (for proprietary ZA) or £251 (given the availability of generic alternatives). These additional costs and the small but positive change in QALYs in favour of ZA resulted in ICERs of £42,047 for the proprietary product or £8005 for the alternative generic-based price. Whether or not the addition of ZA to chemotherapy represents a cost-effective use of resources depends largely on the acquisition cost of a 4-mg dose of ZA. In the likely case that NHS trusts pay less than £98 for 4 mg of ZA, the ICER for ZA is below £20,000 per QALY, and thus ZA represents a cost-effective option at this ceiling ratio.

Chapter 6 Conclusion

Implications for health care

Docetaxel appears to prevent patients with relapsing bone disease from developing skeletal complications. Its use improves QoL and it should remain a component of the treatment options for men with mCRPC. Sr-89 showed modest benefits at a modest cost, resulting in an ICER lower than £20,000 per QALY, though it is likely that this radioisotope has now been superseded, in particular by the recently licensed radium-223. ZA reduced serious skeletal complications at a modest additional cost and showed a small gain in QALYs. Analysis using generic ZA resulted in a low additional cost of £251 and, coupled with the gain in QALYs, showed an ICER below the commonly cited value of £20,000 per QALY.

Recommendations for research

Further modelling of the costs of therapy using Hospital Episode Statistics data is desirable and we plan to complete this. Further research into the use of ZA (and other bone-targeting therapies) with newer prostate cancer therapies is desirable.

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GE Healthcare Ltd offered a trial discount of 5% for the purchase of a single dose of Metastron® (Sr-89) per patient for patients entered into the TRAPEZE trial.

Contribution of authors

Nicholas James was the chief investigator and lead author.

Sarah Pirrie was the trial statistician and a member of the TMG and contributed to study oversight, review of protocol changes and editorial review of the manuscript.

Ann Pope, **Darren Barton**, **Duncan McLaren**, **Joe O' Sullivan**, **Chris Parker**, **Emilio Porfiri**, **John Staffurth**, **Andrew Stanley**, **James Wylie** and **Lucinda Billingham** and were members of the TMG and contributed to study oversight, review of protocol changes and editorial review of the manuscript.

Lazaros Andronis led on the economic aspect of the study.

Lazaros Andronis and **Ilias Goranitis** analysed the health economics data and wrote *Chapter 4* of this report, in addition to contributing to editorial review of the manuscript.

Stuart Collins, who was trial statistician up until his premature death in 2011, was also a member of the TMG.

Duncan McLaren and **James Wylie** were primary investigators in centres contributing more than 10% of the trial patients. They also contributed to editorial review of the manuscript.

Sharon Beesley, **Alison Birtle**, **Janet Brown**, **Prabir Chakraborti** and **Martin Russell** were primary investigators from high-recruiting centres who also contributed to editorial review of the manuscript.

Other contributors

Mr Kaisheng Wen, Senior Research Fellow, University of Birmingham School of Cancer Sciences, for analysis of proteomic plasma samples for the p1NP biomarker.

Publications

James ND, Pirrie S, Barton D, Brown JE, Billingham L, Collins SI, *et al.* Clinical outcomes in patients with castrate-refractory prostate cancer (CRPC) metastatic to bone randomised in the factorial TRAPEZE trial to docetaxel (D) with Sr-89 (Sr-89), zoledronic acid (ZA), neither or both. Oral abstract presented at the Meeting of the American Society of Clinical Oncology, Chicago, IL, 3 June 2013.

James ND, Pirrie S, Barton D, Brown JE, Billingham L, Collins SI, *et al.* Clinical outcomes in patients with castrate-refractory prostate cancer (CRPC) metastatic to bone randomised in the factorial TRAPEZE trial to docetaxel (D) with Sr-89 (Sr-89), zoledronic acid (ZA), neither or both. Oral and poster abstract presented at National Cancer Research Institute, Liverpool, 4 November 2013.

James ND, Pirrie SJ, Pope AM, Barton D, Andronis L, Goranitis I, *et al*. Clinical outcomes and survival following treatment of metastatic castrate-refractory prostate cancer with docetaxel alone or with strontium-89, zoledronic acid, or both: the TRAPEZE randomized clinical trial. *JAMA Oncol* 2016;**2**:493–9.

Andronis L, Goranitis I, Pirrie S, Pope A, Barton D, Collins S, *et al.* Cost-effectiveness of zoledronic acid and strontium-89 as bone protecting treatments in addition to chemotherapy in patients with metastatic castrate-refractory prostate cancer: results from the TRAPEZE trial (ISRCTN 12808747) [published online ahead of print June 3 2016]. *Brit J Urol Int* 2016.

Data sharing statement

At the time of publication there are no plans by the authors to formally publish the full anonymised study data set on a publically assessable database/study archive system. Any requests for additional information, access to data (TRAPEZE anonymised clinical data set) should be submitted in writing to the TRAPEZE Management Team at the Cancer Research Clinical Trials Unit (CRCTU), University of Birmingham, Birmingham, UK (at crctu-generalenquiries@trials.bham.ac.uk).

The CRCTU are supportive of data sharing and will endeavour to assist external investigators who wish to share clinical trial data. Given the diversity of the CRCTU portfolio, all requests for data sharing are dealt with on a case-by-case basis and as specified below.

The request should clearly document the following:

- the scientific rational of the proposal
- aims and objectives
- outcome measures
- data variables required
- how the data will be analysed
- indicate what acknowledgement the Trial Management Group and the CRCTU will receive on any publications resulting from the work.

In some circumstances investigators may also be asked to complete a CRCTU New Business Committee form.

On receipt of a valid request to share data the CRCTU will ensure that:

- external parties and trial oversight committees (e.g. Trial Steering Committee) are supportive of the request
- the necessary legal, ethical and regulatory permissions to allow data sharing are in place
- completely anonymised data can be supplied
- there is sufficient resource within the CRCTU to deal with the request.

If the above conditions are met the CRCTU will provide the requested data. In some circumstances this may be subject to a Data Sharing Agreement being put in place.

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Appendix 1 Trial protocol

A randomised phase II / III study of Docetaxel plus Prednisolone vs. Docetaxel plus Prednisolone plus Zoledronic acid vs. Docetaxel plus Prednisolone plus Strontium-89 vs. Docetaxel plus Prednisolone plus Zoledronic acid plus Strontium-89 in Hormone Refractory Prostate Cancer metastatic to bone.

Trapeze

Taxane

Radioisotope

Zoledronic acid

Phase II/III Efficacy and Safety Clinical Trial in Hormone Refractory Prostate Cancer

Protocol

Version 11, 17 February 2012

Protocol Number: PR2100

EudraCT Number: 2004-002295-41

HTA 06/303/205

ISRCTN 12808747

NCRN National Cancer Research Network

NHS Health Technology Assessment programme funded project www.hta.ac.uk

UNIVERSITY OF BIRMINGHAM

SUMMARY OF AMENDMENTS

Protocol Version No. /Date	Brief description of previous amendments
Trapeze, Phase II Version 4 (01/09/2004) Version 5 (23/03/2005)	• Change to the eligibility criteria to enable patients to enter the study without the need for a confirmation prostate biopsy if they have confirmed bone disease with a PSA value ≥ 100ng/ml. • Change to wording of baseline and post chemotherapy assessment requirements will allow centres to take part in the study without the need to perform clinical procedures if local facilities are not available.
Version 6 (07/06/2005)	• Safety amendment to clarification of zoledronic acid dose procedures to comply with SmPC.
Version 7 (04/05/2007)	• Changes to the inclusion criteria clarified patient eligibility regarding abnormal ALT and AST levels. • The requirement for a confirmed Serum Testosterone blood test was removed from the screening procedures. • A new entry criteria question was added to ensure that at time of study entry all patients were fit enough to receive any of the trial treatments, in the opinion of the investigator. • Clarification of administration sequence of trial treatments.
Trapeze, Phase III Version 8 (24/09/2008)	• The majority of the changes related to the transition from a phase II to a phase III clinical trial, covering trial infrastructure, data collection procedures and statistical considerations. These changes had no direct impact on patient participation or safety, but did increase the maximum number of chemotherapy cycles from 6 to10, according to NICE guidelines for docetaxel chemotherapy.
Version 9 (12/04/2011)	• This amendment concerns a statistical redesign of the phase III trial from a 4 arm comparison to a 2 by 2 factorial design to assess treatment efficacy. • Reduction of target recruitment from 1240 (as per version 8 amendment) to 618 evaluable patients. The trial will close to recruitment at the end of February 2012.
Version 10 (25/05/2011)	• This amendment concerns a correction in section 12.2.3 on timing of analysis. We intend to conduct initial analysis once all patients have at least 1 year's follow-up not 2 years as previously stated.

Version 11 (17/02/2012)	Substantial amendments : • Changing the requirement for both ALT and AST to be tested – only one of them needs to have been performed. • Change of definition for skeletal related event-free interval and pain progression-free interval, and removal of the event of death as a skeletal related event and element of pain progression criteria. Non-substantial amendments : • Clarification of prophylactic anti-emetic for nausea/vomiting due to chemotherapy, and permission to use local protocols that coincide with off-study practice. • Updating of Deputy Clinical Co-ordinators details. • Additional safety information for zoledronic acid administration. • Various typographical corrections and clarifications of existing text.

TRIAL MANAGEMENT GROUP

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RANDOMISATION

CLOSING TO RECRUITMENT AT 5PM ON WED 29 FEBRUARY 2012

Mon-Fri 9.00–5.00

Tel: [redacted] or [redacted]

Fax: [redacted] (24hrs) or [redacted]

CLINICAL QUERIES

Clinical queries during office hours should be directed to the Clinical Co-ordinator,

Professor N James, on Tel: [redacted]

or an appropriate member of the Trial Management Group*.

Out of hours, please call Queen Elizabeth Hospital switchboard on Tel: [redacted] and ask to bleep Professor N James, Clinical Co-ordinator.

CHIEF INVESTIGATOR SIGNATURE PAGE

A randomised phase II / III study of Docetaxel plus Prednisolone vs. Docetaxel plus Prednisolone plus Zoledronic acid vs. Docetaxel plus Prednisolone plus Strontium-89 vs. Docetaxel plus Prednisolone plus Zoledronic acid plus Strontium-89 in Hormone Refractory Prostate Cancer metastatic to bone.

TRAPEZE

Version 11, 17 February 2012

This Protocol is approved by :

Professor Nicholas James, Chief Investigator

Signature : [redacted]

Date : 1st May 2012

INVESTIGATOR SIGNATURE PAGE

I have thoroughly read and reviewed the study protocol:

A randomised phase II / III study of Docetaxel plus Prednisolone vs. Docetaxel plus Prednisolone plus Zoledronic acid vs. Docetaxel plus Prednisolone plus Strontium-89 vs. Docetaxel plus Prednisolone plus Zoledronic acid plus Strontium-89 in Hormone Refractory Prostate Cancer metastatic to bone.

TRAPEZE

I have read and understood the requirements and conditions of the study protocol.

I am aware of my responsibilities as an Investigator under the guidelines of Good Clinical Practice (GCP), the Declaration of Helsinki, local regulations and the study protocol and I agree to conduct the study according to these guidelines and to appropriately direct and assist the staff under my control who will be involved in the study.

I agree to use the study material, including medication, only as specified in the protocol.

I understand that changes to the protocol must be made in the form of an amendment, which has to be approved by the relevant Ethics Committee prior to its implementation.

I understand that any violation of the protocol may lead to early termination of the study.

Investigator's Name: .....

Signature: .....

Date: .....

The Principal Investigator must sign this page and return a copy to the Trapeze Study Office.

PROTOCOL SYNOPSIS

TITLE:	A randomised phase II/III study of Docetaxel plus Prednisolone vs. Docetaxel plus Prednisolone plus Zoledronic acid vs. Docetaxel plus Prednisolone plus Strontium-89 vs. Docetaxel plus Prednisolone plus Zoledronic acid plus Strontium-89 in Hormone Refractory Prostate Cancer metastatic to bone.
STUDY DESIGN:	Randomised Phase II/III clinical trial with 4 different treatment combinations
STUDY OBJECTIVES:	Phase II objective: To compare the four trial arms with respect to feasibility, tolerability and safety Phase III objective: To assess treatments with respect to efficacy within a 2×2 factorial design framework i.e. the trial will compare (i) ZA versus no ZA (stratified for Sr89 use) and (ii) Sr89 versus no Sr89 (stratified for ZA use).

STUDY POPULATION SAMPLE SIZE, INCLUSION & EXCLUSION CRITERIA:	The trial aims to recruit a minimum of 618 evaluable adult male patients with Hormone Refractory Prostate Cancer with:
	
	INCLUSION CRITERIA
	• Histologically/cytologically-proven prostate adenocarcinoma OR multiple sclerotic bone metastases with a PSA≥100ng/ml without histological confirmation.
	• Radiological evidence of metastasis.
	• Fit enough to receive trial treatment.
	• Prior hormonal therapy for prostate cancer.
	• For patients who have received prior hormonal drug therapy:
	  • Flutamide, nilutamide, bicalutamide, cyproterone acetate or stilboestrol must have stopped at least four weeks prior to enrolment and progression must have been demonstrated since cessation.
	  • Estramustine must have stopped at least four weeks prior to enrolment and any adverse events must have been resolved and progression demonstrated since cessation.

	• Documented progression, defined by:
	  • Elevated and rising prostate-specific antigen (PSA).
	  • And/or progression of any unidimensionally or bidimensionally measurable malignant lesion.
	  • And/or at least one new lesion identified on bone scan by radiological assessment of the bone.
	• Life expectancy ≥ 3 months.
	• ECOG performance status 0-2.
	• Adequate haematological function.
	• Adequate renal and hepatic function.
	• Written informed consent.
	
	EXCLUSION CRITERIA
	• Prior cytotoxic chemotherapy for HRPC, other than estramustine monotherapy.
	• Prior radiotherapy to more than 25% of the bone marrow or whole pelvic irradiation.
	• Prior radionuclide therapy for HRPC.
	• Prior treatment with a bisphosphonate for any reason within the previous 2 months.
	• Malignant disease within the previous 5 years, other than adequately treated basal cell carcinoma.
	• Known brain or leptomeningeal metastases.
	• Symptomatic peripheral neuropathy ≥ grade 2 (NCI CTC).
	• Concurrent enrolment in any other investigational clinical trial.
	• Treatment with any other investigational compound within the previous 30 days.
	• Any condition, which, in the opinion of the investigator, might interfere with the safety of the patient or evaluation of the study objectives.

1 BACKGROUND

1.1 Hormone-Refractory Prostate cancer

Prostate cancer is the commonest cancer in men in the UK and other industrialised countries and one of the leading causes of death.

Although adenocarcinoma of the prostate most often presents as local (stage T1 or T2) disease, in which the malignancy is confined to the prostate, a significant proportion of patient's progress despite initial treatment with ablative surgery or radiotherapy, often in combination with hormonal therapy.

Metastatic disease, which is reliably predicted by increasing levels of prostate-specific antigen (PSA), is usually treated by androgen-withdrawal, which can be achieved surgically, by bilateral orchidectomy (castration), or medically, with LHRH-receptor agonists. Initial response rates are very high, but recurrence is almost inevitable and median survival once androgen ablation has failed is typically 12-18 months in the presence of metastatic disease.

Treatment of hormone-refractory prostate cancer (HRPC) is essentially palliative and options include further hormone manipulations, systemic chemotherapy, bisphosphonates, radio-isotopes as well as traditional palliative therapies such as radiotherapy to symptomatic areas and surgery for obstructive symptoms or bone problems such as fracture or spinal cord compression. There are a large number of trials of new agents currently underway in metastatic HRPC (mHRPC) and it is likely that additional effective treatments will become available in the coming years, though it is unlikely that they will supplant the current options (cf herceptin in metastatic breast cancer). James *et al.* published review of the management of metastatic HRPC in 2006[1].

Bone pain is often the most debilitating component of metastatic prostate cancer, occurring in around 80% of cases of HRPC. Current systemic treatment strategies include chemotherapy, bisphosphonates and bone-seeking radioisotopes, including Sr89 and samarium-153. Focal irradiation to bone pain for solitary, painful bone metastases is an effective palliative strategy and may be supplemented by hemibody irradiation for the palliation of widespread metastases.

1.2 Use of Docetaxel (Taxotere) In HRPC

Mitozantrone has previously been compared to steroids alone in the palliative treatment of patients with symptomatic metastatic HRPC and been shown to improve quality of life and progression-free, but not overall, survival[2;3]. More recently, taxane-based chemotherapy has been shown to produce much higher biochemical response rates than mitozantrone and two landmark trials using docetaxel-based therapies published in 2004 demonstrated improved overall survival and quality of life compared to mitozantrone in two trials using docetaxel-based therapies[4;5]. Low numbers of treatment-related deaths occurred in both the docetaxel arms and in the mitozantrone control arms with no clear or consistent differences between arms. Generally the docetaxel regimens were reasonably well-tolerated and the adverse event profiles were similar to those seen with other cytotoxic regimens.

On the basis of these trials, a three-weekly schedule of docetaxel plus prednisolone for up to 10 cycles has emerged as the standard of care for mHRPC and has been approved by the National Institute for Health and Clinical Excellence (NICE) for this purpose in 2006. In this trial we propose to limit initial docetaxel to 6 cycles (the mean number of cycles on the TAX 327 licensing study[6] was 7) to ensure the feasibility of the delivery of Sr89 (see below). Patients still responding to docetaxel (stable disease or better response to therapy, as determined by the treating clinician) after 6 cycles will be eligible to receive a further 4 cycles of chemotherapy.

1.3 Use of Bisphosphonates in HRPC

The use of bisphosphonates in oncology has increased over the last decade, although they remain the subject of controversy in prostate cancer. Bisphosphonates inhibit bone catabolism by reducing the numbers of functioning osteoclasts and have been an established treatment for osteoporosis and similar conditions for many years and more recently have been used to manage bone metastases in breast cancer[7]. In addition, some bisphosphonates, for example zoledronic acid, but, interestingly, *not* clodronate, arrest cell-proliferation, induce apoptosis, and inhibit the growth-factor stimulation of cultured prostate cancer cells[8].

A number of bisphosphonates have been examined in prostate cancer including pamidronate, clodronate and zoledronate. Pamidronate failed to show benefit in a randomised study[9,] A large randomised, placebo controlled study (MRC PR05) reported that clodronate improved the pain-free survival period and overall survival period for patients with metastatic prostate cancer compared with placebo, although the benefits did not achieve statistical significance (i.e. $p>0.05$)[10]. Further, the authors conducting this study reported more gastrointestinal side effects, increased lactose dehydrogenase and required more trial dose modifications, although patients in the clodronate group

were significantly less likely to experience deterioration in their performance status (HR 0.71, 95% confidence interval 0.56 to 0.92, p=0.008). A trial combining clodronate with mitozantrone failed to show any additional palliative benefit from adding this agent to chemotherapy alone[11] and we thus felt that a further study combining this agent with chemotherapy was unwarranted.

Since the publication of the MRC PR05 study, more potent bisphosphonates have been evaluated in mHRPC. The most widely studied has been zoledronate, which has a 40-850 fold higher potency than clodronate in preclinical models of bone resorption[12]. It has also been shown to be more effective than pamidronate (90mg) in controlling malignant hypercalcaemia[13]. In addition, zoledronate has also demonstrated direct anti-cancer activity, including inhibition of proliferation of breast cancer and prostate cancer cells *in vitro*[14].

In randomised studies of mHRPC, zoledronate has been shown to delay, or prevent, skeletal related events (SREs: defined as pathological fracture, spinal cord compression, hypercalcaemia, radiotherapy for bone pain)[15]. However, the drug is administered intravenously every four weeks; this has significant resource implications for oncology or urology departments in terms of both drug costs and clinical time. In the UK, use of this agent is patchy and funding is controversial, for example, the Scottish Medicines Consortium recommended that zoledronate should not be used in mHRPC without further evidence of effectiveness. Previous studies with another bone-targeting agent, Sr89 (see below), have suggested that overall healthcare costs are less with use of Sr89 than with alternative means of palliation. As some of the complications of bone disease are catastrophic for both the patient and the Health Service (e.g. spinal-cord compression leading to paralysis), a strategy of prevention with an expensive agent may well prove to be better than a cheaper alternative in terms of overall quality of life, as well as cheaper overall for the NHS. However, the use of zoledronate requires further evaluation, hence the inclusion of this agent in the trial.

1.4 Strontium-89 (Sr89)

Sr89 is a bone-seeking radionuclide. It is a pure ß-emitter with a half-life of 50 days, has a high uptake in osteoblastic metastases, and remains in tumour sites for up to 100 days. Palliation of bone pain arising from widespread bony metastases may be affected by the intravenous administration of radionuclides that target bone metabolism, for example Sr89, samarium-153 and phosphorous-32. Of these, Sr89 is the most widely used, providing pain-relief in up to 80% of patients, and complete freedom from pain in approximately 10%, for periods that can exceed three months[16;17]. In a randomised controlled phase III trial, the combination of Sr89 injection and external beam radiotherapy improved pain relief, delayed disease-progression and enhanced some quality of life measures compared with external beam radiotherapy alone[18]. However, another phase III randomised controlled trial has suggested that, in some patients, systemic Sr89 may be inferior to local field radiotherapy in terms of survival (11.0 versus 7.2 months, p=0.0457)[19]. The selection of

patients has a significant impact on outcome, response and duration of response to radionuclide therapy, as bone pain palliation is reduced in those with widespread metastatic disease or have a short life expectancy[20;21]. Consequently, the use of radionuclides appears to be optimal at an early stage in disease management. However, their efficacy is reduced or lost with repeated use and over-treatment can also lead to irreversible pancytopenia. Both Sr89 and samarium-153 are only available to a minority of NHS patients. There is some evidence that Sr89 may reduce overall health care costs compared to standard methods of delivering radiotherapy[22].

The benefit of Sr89 in combination with chemotherapy has been evaluated in one small, randomised phase II trail in which 103 HRPC patients received induction therapy with ketoconazole and doxorubicin alternating with estramustine and vinblastine. Seventy two patients who were responders or clinically stable were then randomised to receive doxorubicin either with or without Sr89[23]. Median survival was significantly better in the Sr89 arm (27.7 months vs 16.8 months, p = 0.0014). This intriguing trial has not been repeated and forms the basis for the docetaxel plus Sr89 treatment arms in this study.

1.5 Management of Osteoporosis

Patients eligible for the study will be at risk of osteoporosis in view of their previous therapy (androgen deprivation, possible steroid exposure, age) as well as from some on-study therapies (steroids, docetaxel). Osteoporosis should be considered in the causality of any skeletal related event (SRE) and should be investigated where appropriate. A bone density ancillary/sub-study forms part of this trial. As the results of this sub-study are determined by planned interim analysis, it is possible that further recommendations on the management of osteoporosis in this patient group may be made later in the trial.

1.6 Guidelines for Study Design in HRPC

A consensus group of leading investigators in HRPC formulated recommendations for clinical trial design, in order to improve the evaluation of new agents and combinations (Bubley *et al.,*[24]). The recommendations included eligible patient groups and PSA-based response criteria which have been adopted in this study.

2 RATIONALE

HRPC (Hormone Refractory Prostate Cancer) with metastases is uniformly rapidly fatal and improved therapies are desperately needed. Docetaxel (Taxotere®) has been shown to improve survival in patients when compared against mitoxantrone in a recent phase III randomised clinical trial in patients with HRPC[4] and its favourable toxicity profile allows for combination with other agents.

The beneficial effects of bisphosphonates on bone resorption make zoledronic acid a suitable choice for combination with docetaxel, leading to fewer SREs and improved palliation in HRPC. Furthermore, as bone disease is often the principal cause of morbidity in HRPC, improved bony outcomes may also impact overall survival.

Sr89 also has beneficial effects on bone metastases but acts by a different mechanism from bisphosphonates, raising the possibility of an additive benefit when the two are co-administered. In addition, one small randomised trial[23] showed a statistically and clinically significant advantage to the addition of Sr89 to chemotherapy in HRPC.

This study therefore seeks to assess whether the addition of Sr89 or zoledronic acid offers a significant benefit in combination with docetaxel and prednisolone in HRPC.

3 STUDY OBJECTIVES AND OUTCOMES

The trial incorporates both phase II and phase III components, each with specific objectives and employing several outcome measures (see Table: section 3.2).

3.1 Study Objectives

3.1.1 Phase II

The primary objective of the phase II component is to assess the feasibility, tolerability and safety of the four treatment arms.

3.1.2 Phase III

The phase III component of the trial will assess treatments within a 2x2 factorial design framework i.e. the trial will compare (i) ZA versus no ZA (stratified for Sr89 use) and (ii) Sr89 versus no Sr89 (stratified for ZA use). Each of these treatment comparisons will be made in terms of clinical efficacy, with primary outcome clinical progression-free survival time, and health economic outcomes. In addition, the trial will assess if there is any association between biomarkers and clinical outcomes.

3.2 Study Outcomes

Phase	Primary	Subsidiary	Ancillary measures and exploratory outcomes
II	• Feasibility, tolerability and safety in terms of cycles of docetaxel and prednisolone with zoledronic acid and/or Sr89 received, cycle delays, dose reductions and toxicity	• Clinical progression-free survival • Skeletal-related event- free survival • Pain progression-free survival • Overall survival • Costs • Quality of life	• Changes in bone mineral density (sub-study) • Biological profiling for prognostic and predictive indicators (sub-study) • PSA-related outcomes • Patient-reported pain-related outcomes
III	• Clinical progression-free survival • Cost and cost-effectiveness	• Skeletal-related event-free survival • Pain-progression–free survival • Overall survival • Quality of life • Toxicity	• Changes in bone mineral density (sub-study) • Biological profiling for prognostic and predictive indicators (sub-study) • PSA-related outcomes • RECIST criteria-related outcomes • Patient-reported pain-related outcomes.

4 STUDY DESIGN

4.1 Study Summary

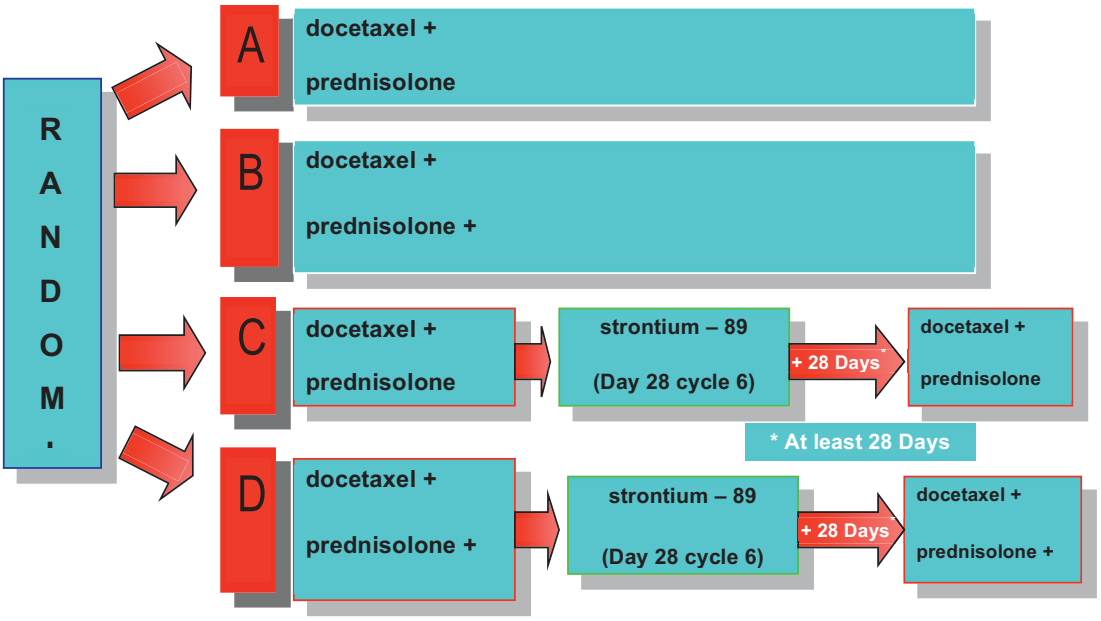

Figure 4.1: Schematic representation of Trapeze study : NB After completion of combined chemotherapy & zoledronic acid cycles on Arms B & D, zoledronic acid is to be administered at four-weekly intervals. At radiological bone progression or at pain progression the local investigator may choose to continue it.

Patients are assessed every three weeks during the study treatment period (during chemotherapy cycles 1-6 and cycles 7-10). After treatment, patients receive monthly follow-up visits for the first three months, with follow-up visits every three months thereafter, until the patient dies or is withdrawn from the study.

All patients will receive a clinical assessment (section 9.3) at the end of cycle 6 (this is the end of the Primary Treatment Period), irrespective of treatment arm.

** In Arms C and D a minimum of 28 days between the date of Sr89 administration and day 1 of cycle 7 of chemotherapy is required. If cycle 7 (day 1) of chemotherapy is delayed and cannot be administered, for any reason, within 8 weeks (56 days) of the date of Sr89 administration then the patient is considered to be 'off–study treatment'. Thereafter, all additional therapy, including any additional docetaxel cycles, will be considered as off-study therapy for the purposes of the trial.

4.2 Study Size

The trial requires 412 events and it is anticipated that a total of 588 patients will need to be recruited to observe this number of events at one year follow-up. We aim to recruit a minimum of 618 evaluable patients which allows for 5% dropout. (see section 12.2 for justification of sample size).

5 STUDY POPULATION

5.1 Inclusion Criteria

- Age ≥ 18 years
- Histologically / cytologically proven prostate adenocarcinoma OR multiple sclerotic bone metastases with PSA≥ 100ng/ml without histological confirmation.
- Radiological evidence of bone metastasis.
- Fit enough to receive trial treatment.
- Prior hormonal therapy for prostate cancer:
    - Bilateral orchidectomy, AND/OR medical castration by LHRH agonist therapy (if LHRH agonist therapy alone, this therapy should be continued).
- For patients who have received prior hormonal drug therapy:
    - Flutamide, nilutamide, bicalutamide, cyproterone acetate or stilboestrol must have stopped at least four weeks prior to enrolment and progression must have been demonstrated since cessation;
    - Estramustine must have stopped at least four weeks prior to enrolment, any adverse events must have been resolved and progression must have been demonstrated since cessation.
- Documented progression, defined by one of the following:
    - Elevated and rising prostate-specific antigen (PSA):
        - PSA > 5ng/ml;
        - Progressive rise in PSA, defined as two consecutive increases in PSA documented over a previous reference value (measure 1). The first increase in PSA (measure 2) should occur a minimum of one week from the reference value (measure 1). This increase in PSA should be confirmed (measure 3) after a minimum of one week. If the confirmatory PSA value (measure 3) is less than the previous value, the patient will still be eligible for the trial provided the next PSA (measure 4) is found to be greater than the second PSA (measure 2). The final sample must have been taken within 28 days of enrolment.
    - And/or progression of any uni-dimensionally or bi-dimensionally measurable malignant lesion
    - And/or at least one new lesion identified on bone scan.
- Life expectancy ≥ 3 months.
- ECOG performance status 0-2.
- Adequate haematological function:
    - Haemoglobin ≥ 10g/dl
    - Neutrophil count ≥ 1.5×10^9/l

- Platelets $\geq 100 \times 10^9$/l
- Adequate renal and hepatic function:
  - Serum creatinine $\leq 1.5 \times$ upper limit of normal
  - Transaminases (ALT, AST or both) $\leq 1.5 \times$ upper limit of normal (unless related to hepatic metastatic disease, where patients may be entered after discussion with one of the Clinical Co-ordinators)
  - Serum bilirubin $\leq 1.5 \times$ upper limit of normal
- Written informed consent.

5.2 Exclusion Criteria

- Prior cytotoxic chemotherapy for HRPC, other than estramustine monotherapy.
- Prior radiotherapy to more than 25% of the bone marrow, or whole pelvic irradiation.
- Prior radionuclide therapy for HRPC.
- Prior treatment with a bisphosphonate for any reason within the previous two months.
- Malignant disease within the previous five years, other than adequately treated basal cell carcinoma.
- Known brain or leptomeningeal metastases.
- Symptomatic peripheral neuropathy $\geq$ grade 2 (NCI CTC).
- Concurrent enrolment in any other investigational clinical trial.
- Treatment with any other investigational compound within the previous 30 days.
- Any condition, which, in the opinion of the investigator, might interfere with the safety of the patient or the evaluation of the study objectives.

6 STUDY TREATMENT

6.1 Study Drug Administration

All four study treatments are IMPs.

6.1.1 Docetaxel

Docetaxel will be administered by intravenous injection in accordance with the instructions in the Summary of Product Characteristics (SmPC) at a dose of 75 mg/m^2 (up to a maximum dose of 165 mg) on day one of the study treatment period and then every three weeks thereafter up to a maximum of 10 cycles.

NOTE: Patients with a body surface area (BSA) greater than 2.2m^2 should be dosed as though they have a BSA of 2.2 m^2. No “ideal” weight should be used for BSA calculations.

6.1.2 Prednisolone

Prednisolone 10mg daily will be given until the completion of chemotherapy, not being interrupted for administration of Sr89. Additional dexamethasone should be given pre- and post-docetaxel infusion to suppress allergic reactions. At the end of chemotherapy treatment, Prednisolone should be tapered off starting 3 weeks from the last administration of docetaxel.

6.1.3 Zoledronic acid

Zoledronic acid will be administered intravenously as a 15 minute infusion in accordance with the instructions in the SmPC at the recommended dose (detailed in the dose table below), every three weeks up to the end of chemotherapy and thereafter monthly. Renal function should be closely monitored throughout the zoledronic acid treatment period.

Serum Creatinine measurements: Serum creatinine should be measured at baseline and within 48 hours prior to every administration of zoledronic acid.
Serum Electrolytes and FBC: Serum electrolytes including calcium, phosphate and magnesium should also be measured prior to each infusion.

Pre-treatment Creatinine Clearance (ml/min)	Zoledronic acid Recommended Dose	Volume of concentrate solution for infusion
>60	4.0 mg	5.0 ml
50-60	3.5 mg	4.4 ml
40-49	3.3 mg	4.1 ml
30-39	3.0 mg	3.8 ml

Patients must also be administered an oral calcium supplement of 500 mg and 400 IU vitamin D daily. These doses are available as a combination tablet. When docetaxel and zoledronic acid are both administered, the recommended sequence of drug administration is the docetaxel infusion prior to zoledronic acid infusion.

Patients must be evaluated prior to and following the administration of the zoledronic acid infusion to ensure that they are adequately hydrated.

If the patient is scheduled to receive a dose of Sr89 (as per study arm, or at any time during the post-study treatment period whilst receiving zoledronic acid), the calcium and vitamin D supplements must be discontinued three weeks before and recommenced four weeks after the Sr89 injection.

Prior to treatment with zoledronic acid, dental examination with appropriate preventive dentistry should be considered for patients with poor dentition. While on treatment these patients should avoid invasive dental procedures if possible. For patients requiring dental surgery, for example tooth extraction, zoledronic acid should be temporarily discontinued prior to dental work and recommenced only when the wound has healed thoroughly.

6.1.4 Strontium-89 (Sr89)

Sr89 will be administered intravenously in accordance with the instructions in the SmPC, as a single dose of 150 MBq given at day 28 after day one of cycle 6, subject to satisfactory recovery of marrow function.

6.2 Planned Interventions

6.2.1 Arm A: Control – Docetaxel plus prednisolone

Docetaxel 75 mg/m^2 (up to a maximum dose of 165 mg) administered intravenously on day one of study treatment plus prednisolone 10mg daily, every three weeks for a maximum of 10 cycles or until disease-progression (as defined by the treating clinician), patient withdrawal, or associated treatment toxicity. It is recommended that all 10 cycles of chemotherapy are administered subject to the above; however, the local clinician can decide to stop therapy at any time for any reason. The reason for discontinuation of therapy must be recorded on the Case Report Form (CRF).

6.2.2 Arm B: Docetaxel plus prednisolone plus zoledronic acid

Docetaxel 75 mg/m^2 (up to a maximum dose of 165 mg) administered intravenously on day one of study treatment plus prednisolone 10mg daily. Zoledronic acid will be administered intravenously at

a dose of 4 mg every three weeks on day one of the chemotherapy cycle up to the end of chemotherapy, and thereafter every four weeks as clinically indicated, or until disease-progression or other discontinuation criteria outlined in Section 8. Patients treated with zoledronic acid will also receive vitamin D and calcium supplements throughout treatment.

6.2.3 Arm C: Docetaxel plus prednisolone plus Sr89

Docetaxel 75 mg/m^2 (up to a maximum dose of 165 mg) administered intravenously on day one of study treatment plus prednisolone 10mg daily, every three weeks thereafter for 6 cycles. At day 28 after the administration of cycle 6 of docetaxel, subject to satisfactory haematological and clinical parameters, Sr89 will be administered as a single dose of 150 MBq. After at least four weeks (28 days) and within 56 days after the Sr89 administration (provided bone marrow function has adequately recovered), the additional chemotherapy cycles (cycles 7-10) will be given until disease-progression (as defined by the treating clinician), patient withdrawal or associated treatment toxicity. It is recommended that all 10 cycles of chemotherapy are administered subject to the above; however the local clinician can decide to stop therapy at any time for any reason.

6.2.4 Arm D: Docetaxel plus prednisolone plus Zoledronic acid plus Sr89

Docetaxel 75 mg/m^2 (up to a maximum dose of 165 mg), prednisolone 10mg daily and Sr89 150 MBq will be administered as described above for Treatment Arm C. In addition, zoledronic acid will be administered intravenously at a dose of 4 mg every three weeks up to the end of docetaxel chemotherapy, and thereafter every four weeks as clinically indicated or until disease progression (as defined by the local clinician). The zoledronic acid dose on day 28 post-chemotherapy, will be omitted and patients will discontinue the calcium and vitamin D tablets for three weeks before and four weeks after the Sr89 injection.

6.3 Further off-study treatment

All further off-study treatment, i.e. chemotherapy, bisphosphonate and radioisotope therapy, received after study treatment must be captured on the “Concomitant Medication Running Form”. The choice of further treatment is at the discretion of the clinician. However, if clinically indicated the following additional treatments are recommended for all patients:

6.3.1 Zoledronic acid

On development of radiological bone progression or pain progression (as defined in Section 8), patients not randomised to receive zoledronic acid, i.e. treatment arms A and C, should be considered to commence this agent. Patients already on zoledronic acid at radiological bone progression or pain progression can continue with this treatment at the investigator’s discretion.

6.3.2 Strontium-89 (Sr89)

On development of radiological bone progression or pain progression, patients not receiving Sr89, i.e. arms A and B, can receive Sr89 at the investigator's discretion. Patients who have already received Sr89, i.e. arms C and D, can receive further Sr89 at the investigator's discretion, but it is recommended, as per the SmPC, that there is at least a 12 week interval between Sr89 administrations.

6.4 Dose Modification in the Event of Toxicity

6.4.1 General rules

Every effort will be made to administer the full dose regimen to maximise dose-intensity. If possible, toxicities should be managed symptomatically. If toxicity occurs, the appropriate treatment will be used to ameliorate signs and symptoms, including antiemetics for nausea and vomiting, anti-diarrhoeals for diarrhoea, and antipyretics and/or antihistamines for drug fever.

If a patient experiences several toxicities and there are conflicting recommendations, the most conservative dose adjustment will be adopted.

No more than two docetaxel dose reductions will be adopted per patient. If more than two dose reductions are indicated, the patient must go off study.

6.4.2 Docetaxel dose reductions

Doses must be adjusted according to the following:

- Standard dose: 75 mg/m²
- First level dose reduction: 60 mg/m²
- Second level dose reduction: 45 mg/m²

Doses which have been reduced for toxicity must not be re-escalated.

6.4.3 Docetaxel dose delay

A treatment delay of four days or more must be reported in the CRF, specifying the reason for the delay. Treatment may be delayed no more than 14 days to allow recovery from acute toxicity. In case of a treatment delay greater than 14 days, the patient must be withdrawn from the trial and a Withdrawal CRF completed.

6.5 Myelosuppression

6.5.1 Neutropenia and/or its complications

Adverse event	Action to be taken
- Grade 4 neutropenia* for 7 days or more. - Grade 3-4 neutropenia with oral fever ≥38.5°C - Infection* (ie. documented infection with grade 3-4 neutropenia)	If the patient develops one of these adverse events, the next docetaxel infusion must be given with a one-level dose reduction.

* according to NCI-CTCAE

ANC on day of infusion	Action to be taken
≥ 1.5 x 10^9/L	Treat on time: do not reduce the dose
< 1.5 x 10^9/L	Delay maximum 2 weeks Blood counts have to be performed until ANC ≥ 1.5 x 10^9/L. Then treat with a one-level dose reduction. If no recovery (ANC still <1.5 x 10^9/L) after 2 week delay: the patient will be discontinued from study.

6.5.2 Thrombocytopenia

In case of grade ≥3 platelets (NCI-CTCAE), treatment may be delayed for a maximum of 14 days until platelets recover to ≥100 x 10^9/L, following which treatment will be given with a one-level dose reduction.

6.5.3 Allergy (anaphylactic and hypersensitivity reactions)

Hypersensitivity reactions that occur despite pre-medication are very likely to occur within a few minutes of the start of the first or of the second infusion of docetaxel. Therefore, during the first and the second infusions, careful evaluation of the general sense of well-being and of blood-pressure and heart-rate monitoring will be performed for at least the first 10 minutes, so that immediate intervention can occur in response to symptoms of an untoward reaction.

Facilities and equipment for resuscitation must be immediately available: antihistamine, corticosteroids, aminophylline, and epinephrine.

If a reaction occurs, the specific treatment that can be medically-indicated for a given symptom (e.g. adrenalin (epinephrine) in case of anaphylactic shock, aminophylline in case of bronchospasm, etc.) will be instituted. In addition, it is recommended to take the measures listed below:

Mild symptoms: Localised cutaneous reaction, such as: pruritus, flushing, rash.	- Consider decreasing the rate of infusion until recovery from symptoms, stay at bedside - then, complete study-drug infusion at the initial planned rate. At subsequent cycles use the pre-medication outlined in section 6.1.1.
Moderate symptoms: Generalised pruritus, more severe flushing or rash, mild dyspnoea, hypotension with systolic B.P. ≤80 mmHg	- stop study drug infusion - give IV antihistamine and IV corticosteroids (*) - resume study-drug infusion after recovery from symptoms. At subsequent cycles, antihistamines* and steroids* will be given IV, one-hour before infusion, in addition to the pre-medication planned in section 6.1.1.
Severe symptoms: e.g. bronchospasm, generalised urticaria, hypotension with systolic B.P. ≤80 mmHg, angioedema	- stop study-drug infusion - give IV antihistamine and steroids (*). add adrenaline (epinephrine)** or bronchodilators and/or IV plasma expanders if indicated. - Once all signs and/or symptoms of hypersensitivity reaction disappear, study-drug may be re-infused within 24 hours from the interruption, if medically appropriate, and whenever possible. Pre-medication regimen as described in section 6.1.1 is only recommended when study drug is re-infused more than 3 hours after the interruption. During subsequent cycles, dexamethasone will be given at 20mg orally, 24, 18, 13, 7 and 1 hour before study-drug infusion. Additionally diphenhydramine (or equivalent) will be given at 50mg IV 1 hour before study-drug infusion. If a severe reaction recurs, patient will go off protocol therapy, , and a Withdrawal CRF completed.
*antihistamines: *Chlorpheniramine (*) IV 10-20 mg* *or promethazine (*) IM 25–50 mg, max-100 mg* *corticosteroids: dexamethasone or equivalent (*) IV 5-10 mg of dexamethasone* *** Adrenaline (epinephrine): administer standard dose – 500 µg).*	

6.5.4 Nausea/Vomiting

A prophylactic anti-emetic treatment should be given to patients from the first cycle. The use of dexamethasone plus a second anti-emetic such as metoclopramide is recommended. Local protocols that coincide with off study practice are permitted. More aggressive anti-emetic prophylaxis (eg. 5-HT_3 antagonists) should be given to a patient who has experienced grade ≥3 nausea/vomiting in a preceding cycle.

If, despite the appropriate medication, grade ≥3 nausea/vomiting still occurs, reduce the dose of docetaxel by one dose level. Should nausea/vomiting continue or recur at grade ≥3 despite the dose reduction, the patient must go off-study, and a Withdrawal CRF completed.

6.5.5 Diarrhoea

No prophylactic treatment for diarrhoea is recommended from cycle one. However, following the first episode of diarrhoea, the patient should receive symptomatic treatment with loperamide:

- 4 mg following the first episode and then 2 mg following each new episode until recovery of diarrhoea (no more than 16 mg daily).

If diarrhoea grade ≥3 still occurs despite the use of loperamide, reduce the dose of study-drug by one dose level. If despite dose reduction, diarrhoea still occurs at grade ≥3, the patient will go off-study, and a Withdrawal CRF completed.

6.5.6 Stomatitis

Grade ≤2: No change, study chemotherapy should be withheld until resolution to grade ≤1. If grade 3 stomatitis occurs, study drug must be withheld until resolution to grade ≤1. Treatment may then be resumed, but the dose of study drug must be reduced by one dose level for all subsequent doses.

In case of grade 4 stomatitis, the patient will go off study, and a Withdrawal CRF completed.

6.5.7 Peripheral neuropathy

In case of symptoms or signs experienced by the patient, dose modification should be performed as follows:

- Grade ≤1: no change.
- Grade 2: re-treat with a one-level dose reduction (no further dose reduction is planned).
- Grade ≥3: patient will go off study, and a Withdrawal CRF completed.

6.5.8 Skin toxicity

- Grade 0, 1, 2: No change.
- Grade ≥3: delay until grade ≤1, maximum 2 weeks then reduce dose of study drug by one dose level; if no recovery to grade ≤1 within 2 weeks delay, patient will go off protocol therapy, and a Withdrawal CRF completed.

6.5.9 Liver toxicity

In case of increase of ALT and/or AST to >1.5 x ULN or bilirubin to >ULN, delay study drug treatment for up to 2 weeks until ALT and/or AST returned to ≤1.5 x ULN and bilirubin to ≤ ULN. Then re-treat at one dose level lower.

In the case of a patient entered into the study with elevated bilirubin levels (serum bilirubin ≥1.5 × upper limit of normal) as per the eligibility criteria, the criteria detailed in the above paragraph for dose reduction/treatment delay in relation to bilirubin levels for this patient DO NOT apply. In this

case the individual patient's reading at study entry is considered the normal bilirubin level for that individual. Subsequent dose delays and dose reductions are applied as above, if the individual's bilirubin level increases from baseline after cycle 1 of chemotherapy. This is because any increase in the bilirubin level can be considered toxicity from treatment and not related to the underlying disease at baseline.

6.5.10 Docetaxel-induced fluid retention

In case of fluid retention (peripheral oedema and/or effusions) during the treatment with docetaxel, the signs and symptoms should be graded as mild, moderate, severe or life threatening.

NO DOSE REDUCTION IS PLANNED

The patient's body weight will be recorded and followed as frequently as possible to document any weight gain, which could be related to oedema.

Recommended treatment

Treatment should commence when signs and/or symptoms of fluid retention are observed, including weight gain from baseline grade ≥1 not otherwise explained.

Based on the hypothesis of capillary damage due to docetaxel, the following treatment is recommended in case fluid retention occurs: frusemide 20 mg orally once daily.

If the symptoms cannot be controlled adequately i.e. worsening of the fluid retention or spread to another area, the dose of frusemide should be increased to 40 mg. The addition of metolazone orally at the recommended dose together with potassium ± magnesium supplements may be useful.

The clinical tolerance of the patient, the overall tumour response and the medical judgment of the investigator will determine if it is in the patient's best interest to continue or to discontinue the study drug. It is recommended, however, that patients with fluid retention of grade ≥3 severity should be withdrawn, and a Withdrawal CRF completed.

In case it is difficult to make a judgment as to whether an effusion is disease-related or study drug-related, the treatment should be continued until progressive disease in other organs is documented, and provided there is no worsening of the effusion during treatment.

6.5.11 Docetaxel-induced hyperlacrimation

The excessive lacrimation (epiphora) seen in some patients receiving docetaxel appears to be related to cumulative dose (median ~300 mg/m^2) and resolves rapidly after treatment discontinuation. Excessive lacrimation seems to be the result of a chemical conjunctivitis and/or chemical inflammation (with oedema) of the lachrymal duct epithelium (producing a reversible lachrymal duct stenosis). If epiphora persists patients should be referred to an Ophthalmologist.

In patients experiencing clinically significant hyperlacrimation, the following approach is recommended:

NO DOSE REDUCTION PLANNED

Frequent instillation of artificial tears.
Prescribe a steroid ophthalmic solution (e.g. prednisolone acetate): 2 drops each eyelid for 3 days starting the day before docetaxel administration in patients without a history of herpetic eye disease.

6.5.12 Zoledronic acid and renal impairment

Please refer to section 6.1.3.

6.5.13 Hypersensitivity to zoledronic acid

If hypersensitivity occurs treatment should be discontinued, or continued with the use of anti-histamines, at the discretion of the treating clinician.

6.5.14 Osteonecrosis of the jaw and zoledronic acid

Long-term use (i.e. >24 months) of zoledronic acid use has been linked to osteonecrosis of the jaw (ONJ). This is of particular concern in patients who have dental disease. If a patient develops ONJ then their zoledronic acid should be immediately and permanently discontinued.

6.5.15 Strontium-89 (Sr89)

This should be omitted if there is inadequate marrow reserve (Hb ≤10 g/dL, neutrophils $\leq$1.5 x 10^9/L, platelets $\leq$100 x 10^9/L). There will be no dose reduction : Sr89 must be given at full-dose if it is given as trial treatment.

7 STUDY ORGANISATION

7.1 Duration of Study

It is anticipated that the study will involve up to 50 centres. At a mean recruitment rate of approximately 15 patients per month, accrual should be feasible in the previously estimated 6-year time span. The primary treatment period (i.e. the first 6 cycles of chemotherapy) for each patient will last 18 weeks in arms A and B (the arms that are not randomised to receive Sr89) and 22 weeks in arms C and D (the arms which are randomised to receive Sr89). A further 4 cycles of chemotherapy may be given to all patients; continuous for patients in arms A and B and following a break of at least 28 days (and less than 56 days) for those in arms C and D. Following completion of chemotherapy (docetaxel) patients in treatment arms A and C may receive zoledronic acid monthly (every four weeks) at the clinician's discretion. Follow-up visits will initially occur monthly for three months, and subsequently three-monthly until death or withdrawal for any other reason. Patients withdrawn from the study will be followed-up by ONS flagging, which will provide copies of patients' death certificates. For such patients, a withdrawal CRF must be completed. It is estimated that recruitment of participants into the study will be complete by the end of February 2012.

The Trial Management Group (TMG) is responsible for protocol development and initiation of the study. This group forms the basis for the Trial Steering Committee (TSC) who are responsible for monitoring study-progress, amending the study-protocol as required, overseeing the trial conduct and providing information to the Independent Data Monitoring Committee (IDMC). The Cancer Research UK Clinical Trials Unit (CRCTU), School of Cancer Sciences, (formerly within the Institute for Cancer Studies) University of Birmingham, is responsible for the day-to-day running of the study, centre-initiation, reporting to the TSC and IDMC, analysis, and presentation of results. Intellectual property and access to data arising from this trial will be governed by the TSC.

7.2 Site Responsibilities

The Principal Investigator at each participating centre has overall responsibility for the study and all patients entered into the study, but may delegate responsibility to other members of the study team as appropriate. The Principal Investigator must ensure that all staff involved in the trial are adequately trained and that their duties have been logged on the Site Responsibilities Sheet.

7.3 Study Start-Up and Core Documents

Centres wanting to participate in the study should contact the study office to obtain information. The Principal Investigator should then provide the study office with the following core documents and attend an initiation visit or attend an initiation teleconference before the site is activated:

Core Documents:

- The site contact details.
- The University of Birmingham Clinical Study Site Agreement.
- All Investigators and Co-investigators will provide an up-to-date copy of their CV, personally signed and dated, prior to the start of the study. The CV should detail the Investigators' education, training and experience relevant to their role in the study.
- The study-specific Commitment Statement.
- Site Responsibilities Sheet.
- Trust approval letters.

It is the Principal Investigator's responsibility to apply for site-specific assessment for his/her individual site. Once a site has been approved the Principal Investigator will be informed by the Chief Investigator (or one of his team) that site-specific approval has been granted.

7.4 Forms And Data Collection

Data collected on each subject will be recorded by the investigator, or his/her designee, as accurately and completely as possible as soon as the requested information becomes available. The investigator will be responsible for the timing, completeness, legibility and accuracy of the Case Report Form (CRF) and he/she will retain a copy of each completed CRF. The investigator will supply the study office with any required data from such records.

Entries will be made in black ballpoint pen on the CRF provided and must be legible. Any errors should be crossed out with a single stroke, the correction inserted and the change initialled and dated by the investigator or his/her designee. If it is not clear why a change has been made, an explanation should be written next to the change. Typing correction fluid should not be used. Each patient enrolled into the study must have all CRFs completed and signed by the Principal Investigator or his/her designee. This also applies to those patients who failed to complete the study. Data reported on the CRF should be consistent with the source data, or the discrepancies should be explained.

To enable peer review and/or audits from Health Authorities or other regulatory bodies, the Investigator must agree to keep records, including the identity of all participating subjects (sufficient information to link records, e.g. CRFs and hospital records), all original signed Informed Consent

Forms, copies of all CRFs and detailed records of drug disposition. It is the responsibility of the Principal Investigator to ensure that all essential trial documentation and source records (e.g. signed Consent Forms, Investigator and Pharmacy Files, patients' hospital notes, copies of CRFs etc.) at their site are securely retained for at least five years after the end of the trial: participating sites will be sent a letter specifying the permissible disposal date.

7.5 Quality Of Life Data (Sub-study)

Quality of life (QoL) will be assessed using EuroQol EQ-5D and FACT-P, which are patient-completed questionnaires (Appendix 3, 4). Patients will also be asked to complete pain diary sheets during their treatment (Appendix 5). All eligible patients will be asked to consent to both the main trial and also to the QoL part of the trial, as taking part in this part of the trial is optional. QoL questionnaires will be completed at baseline, on treatment (prior to each dose of docetaxel), and at every protocol-defined visit,, including all patient follow-up visits. The patient should be asked to complete the QoL questionnaires prior to consultation with the clinician. It is the intention that in this trial, patients will be asked to complete QoL questionnaires and Pain Diaries from the date of randomisation until death or patient refusal. The completion of these documents is voluntary and should continue throughout patient follow-up (pre- and post-clinical progression) irrespective of any further therapy that an individual patient may receive. All additional therapy post-clinical progression will be recorded in the relevant page of the CRF.

It is essential to explain to the patient that all parts of the QoL questionnaire should be completed as fully as possible. In order to administer these consistently, the QoL questionnaires will be in order and given to the patient in a stapled booklet. Each centre must identify a named individual responsible for administering the QoL questionnaires.

Participation in the QoL sub-study is not compulsory and will not affect the patient's ability to take part in the trial.

7.6 Health Economic Analysis

The economic analysis will be conducted alongside the trial. The main objective of this analysis is to assess the costs and cost-effectiveness across different treatments. The key resource use data will be collected through the CRFs and supplemented by a patient-completed resource-use questionnaire. Health-related QoL will be assessed using the EQ-5D. The EQ-5D is a widely-used, brief, generic utility-based measure of health-related QoL. A utility score will be generated from this questionnaire. Quality-adjusted life-years (QALYs) will be calculated using area under the curve methods. A cost-effectiveness analysis will be conducted in which outcome will be measured as incremental cost per QALY gained within the trial period analysis.

The scope for validating data on resource use by using routine NHS administrative system data will be explored, including obtaining patient consent. Modelling will be required to estimate the cost per life year and per QALY, for sensitivity analysis and also to explore the implications of generalising from the study.

The economic analysis will be undertaken in conjunction with The Health Economics Unit, University of Birmingham, who have extensive experience in such work.

7.7 Biomarkers Data (Sub-study)

The CRCTU will request pathological information at the time of randomisation for all patients entered into the trial. This information will include histology number, location of paraffin-embedded tumour blocks and reporting consultant pathologist. Subject to patient consent, collection of this information will allow for the prospective collection of tissue blocks, which will be analysed at a later date. Immuno-histochemical techniques will be used on tissue sections to test for the presence of biological predictive-markers of treatment benefit (e.g. P53, P27, P20, Ki67, Her2/neu, EZH2).

We will also seek patient consent for the collection and storage of repeat blood samples which can initially be stored at the local centre but ultimately will be sent to CRCTU for future proteomic analysis of known (e.g. PSA, FGS, IGS) and novel protein markers using the expertise within the School of Cancer Sciences in Birmingham and other collaborative centres.

7.8 Computerised Records

Create data – Details of centres and participating staff will be recorded during the study. Patient data records will be created at randomisation and data entered from CRFs during study participation.

Modify and maintain data – Records of centres and participating staff will be modified to maintain accurate details of trial-related personnel and their involvement status. Data from CRFs will be modified to correct any erroneous or missing entries. The reason for these changes will be recorded to facilitate an audit trail.

Archive – At the conclusion of the trial, when all patient data has been collected, and the analysis is complete, all the data stored on the computer system will be archived for 15 years. After trial conclusion, if any audit is required, or new analysis to be performed, the data will be retrieved.

7.9 Monitoring

The study is being conducted under the auspices of the CRCTU according to the current guidelines for Good Clinical Practice. Participating centres will be monitored by CRCTU staff to confirm compliance with the protocol and the protection of patients' rights as detailed in the Declaration of Helsinki.

Participating centres will be monitored by checking incoming forms for compliance against the protocol, consistent data, missing data and timing. Study staff will be in regular contact with centre personnel to check on progress and to deal with any queries they may have.

On-site monitoring will be carried out as required following a study-specific risk assessment and as documented in the study-specific monitoring plan.

8 STUDY PROCEDURES

8.1 Patient Screening

The investigator will provide patients who appear to meet the criteria for participation in the study with information to allow them to make an informed decision regarding their participation. If informed consent is given, the investigator will conduct a full screening evaluation to ensure that the subject satisfies all inclusion and exclusion criteria. If the screening is successful, it is recommended that the patient commences trial treatment within two weeks of randomisation.

8.2 Randomisation of Patients

Randomisation will be undertaken by the CRCTU, School of Cancer Sciences, University of Birmingham.

8.2.1 Stratification

Patients will be randomised to treatment arms in a 1:1:1:1 allocation ratio using a computerised minimisation algorithm. Randomisation will be stratified by centre and ECOG performance status (0,1,2) to avoid imbalance in the four treatment arms.

8.2.2 Randomising a patient

To randomise a patient:

- Obtain the patient's written informed consent to participate in the study.
- Complete the Randomisation Form
- Telephone:

Mon-Fri, 9.00 –5.00
Tel: [redacted] or [redacted]
Fax: [redacted] (24hrs)

The patient will be allocated their treatment and a trial number, which must be noted on the Randomisation CRF. The investigator should send the patients' GP a letter and information sheet indicating their participation in the study.

8.3 Study Treatment Period

Day 1 of the study treatment period is the day on which the first dose of docetaxel is administered and prednisolone commenced. The first 22 weeks is the primary treatment period: 6 cycles of docetaxel +/- Sr89 +/- zoledronic acid, according to the randomisation treatment allocation. A further

4 cycles of docetaxel can then be given according to the details in section 6 of the protocol. This period will be classed as the secondary treatment period. Prednisolone should be tapered off starting 3 weeks from the last administration of docetaxel.

If a patient has been randomised to receive zoledronic acid, this will be continued 4 weekly thereafter until protocol-defined disease progression, patient or clinician withdrawal (for toxicity), or patient choice. Further treatment (including the use of zoledronic acid) after clinical disease progression will be given according to local clinical practice.

8.4 Follow-up Period

The follow-up period begins after the completion of the primary and secondary (if given) treatment periods. Patients are followed-up every month for the first three months and then every three months until death or patient withdrawal for any other reason.

8.5 Discontinuation of Study Treatment

Discontinuation of any study medication(s) must be reported by completing the Withdrawal CRF.

8.5.1 Discontinuation of study docetaxel

A patient should be withdrawn from docetaxel treatment in the event of any of the following:

- Progression due to either:
    - Pain progression (as defined by the local clinician), or
    - Clinical Disease progression, as defined by the local clinician.

      NOTE: biochemical (PSA) progression alone is NOT a reason to discontinue treatment unless the investigator deems it to be in the best interests of the patient.
- Development of a life-threatening and/or irreversible toxicity not manageable by symptomatic care, dose reduction, or dose delay. A maximum of two docetaxel dose reductions are permitted per patient (see Section 6.4.1). A maximum dose delay of 14 days is permitted on each cycle of docetaxel (see Section 6.4.3).
- Administration of any other anti-tumour chemotherapy, radiotherapy or investigational agent during the trial.
- Development of any condition, or occurrence of any event, which, in the opinion of the investigator, justifies discontinuation of treatment.
- Patient's decision to discontinue trial treatment or to withdraw (consent) from other aspects of the trial, e.g. completion of QoL booklets, participation in tumour-block collection or proteomic (blood sample) collection.

8.5.2 Discontinuation of study zoledronic acid

A patient should discontinue on-going zoledronic acid in the event of any of the following:

- Development of any of the toxicities requiring discontinuation as described in section 6.5.12.
- Pain progression or clinical disease progression (as defined by the local clinician). NOTE zoledronic acid may continue to be given (off-study) at the investigator's discretion.
- Development of any condition or occurrence of any event, which, in the opinion of the investigator, justifies discontinuation of treatment.
- Patient's decision to discontinue trial treatment or to withdraw from the trial.

8.5.3 Omission of study Sr89

The planned treatment of Sr89 should be omitted in the event of any of the following:

- Unsatisfactory haematological and clinical parameters as described in section 6.5.14.
- Failure to complete 6 cycles of study docetaxel.
- Development of any condition or occurrence of any event, which, in the opinion of the investigator, justifies discontinuation of treatment.
- Patient's decision to discontinue treatment or to withdraw from the trial.

8.6 Study Completion

A patient will be considered to have completed the study in the event of death or of loss to follow-up.

9 STUDY ASSESSMENTS

9.1 Baseline Assessments

The following must have been done not more than 28 days **prior** to enrolment, with one exception as detailed below:

- Medical history.
- Physical examination.
- ECOG performance status
- Tumour assessment by any or all of: CT scan, MRI scan, bone scan and ultrasound:
    - The trial management team *recommend* that the tumour assessment is performed within 56 days of patient randomisation.
    - The same technique must continue to be used for a given lesion throughout a patient's study course.
    - As per eligibility criteria, radiological evidence of bone metastasis is required for study entry. If a patient has received additional cancer therapy after the radiological imaging, but prior to randomisation into the trial, new imaging is required to confirm that the patient has continued disease involvement of the bone
- Chest X-ray (required if no CT scan of chest) or CT scan.
- Dual energy X-ray absorption scan (DXA) – Bone Density Scan.

(The requirement for a DXA scan may not be required if the participating centre is not taking part in the relevant sub-study, or if a patient has declined to participate in this part of the study).

- Proteomic blood sample (subject to individual investigator site participation)
- Serum PSA.
- Haematology tests: haemoglobin, WBC count, neutrophil count and platelet count.
- Clinical chemistry tests: urea, serum creatinine, potassium, sodium, calcium, magnesium, aminotransferases (AST, ALT or both), alkaline phosphatase, total bilirubin and blood glucose.
- Pain score and analgesic use (see Section 9.5). Both pain and analgesic-use scores will be derived from the record of the week immediately prior to assessment.
- Questionnaires: QoL using EuroQol EQ-5D and Fact-P questionnaires, the resource-use questionnaire.

9.2 Assessments During Study Treatment Period (Cycles 1-10 of Chemotherapy)

The following assessments will be carried out at the indicated intervals during the course of the study:

- Tumour assessment as clinically indicated - each lesion to be assessed using the same technique as used for that lesion at baseline.
- Chest X-ray or CT scan – as clinically indicated.
- Physical examination.
- Serum PSA: immediately prior to each dose of docetaxel, then every 12 weeks during secondary treatment period.
- Proteomic blood sample at end of cycles 2, 4 and 6 of chemotherapy. If further chemotherapy is given (i.e. cycles 7 to 10) then samples will be taken at the end of cycles 8 and 10 (subject to individual investigator site participation).
- Haematology tests (as at baseline): immediately prior to each dose of docetaxel or assessment.
- Clinical chemistry tests (as at baseline): immediately prior to each dose of docetaxel or assessment.
- Pain score and analgesic use: recorded by patient during the week immediately prior to each dose of docetaxel or assessment (see section 9.5).
- QoL using the EuroQol EQ-5D and Fact-P questionnaires, and the resource-use questionnaire: immediately prior to each dose of Docetaxel or assessment.
- ECOG performance status.

9.3 End of Primary Treatment Period Chemotherapy Assessments (ALL Patients)

Following completion of the 6th cycle of protocol-defined therapy, all patients should have the following assessment completed 21 days after receiving cycle 6 docetaxel. The CRF form to complete is titled 'Post Cycle 6 Docetaxel Assessment Form'. This assessment is not required for patients who do not complete 6 cycles of chemotherapy, nor is it required after the last cycle if more than 6.

For patients not randomised to receive Sr89, the following assessments are the same as those normally performed for pre-chemotherapy assessment required for cycle 7 treatment. It is not necessary to repeat any tests for this assessment, only to record it on the above CRF.

- Physical examination.
- ECOG performance status.
- Imaging required if disease progression is suspected either clinically or biochemically.
- Proteomic blood sample (subject to individual investigator participation).
- Haematology tests: (as at baseline).
- Clinical chemistry tests: (as at baseline) including PSA.
- Pain score and analgesic-use (see section 9.5). Both pain and analgesic-use scores will be derived from the record of the week immediately prior to assessment.
- Questionnaires: QoL using the EuroQol EQ-5D and Fact-P questionnaires, resource-use questionnaire.

9.4 Follow-up Assessments

Patients who have clinically progressed, i.e. having pain progressed, date of first skeletal-related event, as described in section 10.1.2, should progress to 3 monthly follow-up.

Table : Patient's pathway post-progression

Type of progression	Discontinue docetaxel
Increasing PSA	No
Tumour (radiology)	Yes
Pain progression	Yes
1st SRE	Only if disease related
Death	-

Please note that withdrawal from trial treatment due to disease progression must be reported on a Disease Progression CRF and not a Withdrawal CRF.

9.4.1 Monthly follow-up, for first three months only

During follow-up the following assessments will be performed every month for the first 3 months only, or until the patient completes or is withdrawn from the trial:

- Haematology tests (as at baseline).
- Clinical chemistry tests (as at baseline) including PSA.
- Pain score and analgesic-use (see section 9.5).
- QoL using EQ-5D and Fact-P questionnaires, resource-use questionnaire.
- Imaging as required. The exact timing of any imaging will be determined by the local clinician, and therefore may not occur at one or more follow-up visits.
- ECOG performance status

9.4.2 Three-monthly follow-up, after first three months:

During follow-up the following assessments will be performed every three months (after the first three-monthly follow-up assessments), until the patient completes, or is withdrawn from, the study:

- Haematology tests (as at baseline).
- Clinical chemistry tests (as at baseline) including PSA.
- Pain score and analgesic-use (see section 9.5).
- QoL using EQ-5D and Fact-P questionnaires, resource-use questionnaire.
- Imaging as required. The exact timing of any imaging will be determined by the local clinician, and therefore may not occur at one or more follow-up visits.
- ECOG performance status.

9.5 Patient Pain Diaries

To enable an exploratory analysis of patient-reported pain outcomes, patients will be asked to complete pain diaries. These diaries will provide a daily record of the pain experienced by a patient and their analgesic intake for the seven day period prior to every protocol-defined visit.

The first diary must be collected after patient consent and prior to the first docetaxel treatment. Thereafter, a diary will be completed for the seven day period prior to the:-

- Start of each subsequent chemotherapy cycle (day 1).
- End of the primary treatment period.
- Follow-up assessment visits, and at every protocol-defined visit thereafter.

The diaries will then be promptly reviewed (ideally with the patient present) for compliance by the investigator or nurse. Any potential problems, i.e. dose of drug missing, will be reviewed and amended by the individual patient (if possible) at this time.

It is intended that the pain diaries will be completed by patients throughout the treatment and follow-up periods of the study, until the occurrence of one of the following: death, loss to follow-up or patient refusal. A patient can decide to stop completing pain diaries at any time without giving a reason. Patient participation in the pain diary sub-study is not compulsory and will not affect the patient's ability to take part in the trial.

Pain-scoring will use both the Present Pain Intensity (PPI) six-point scale (0=no pain to 5 = excruciating pain) from the McGill-Melzack questionnaire and the analgesic score, calculated by a member of the participating centre trial team using the following table :

SCORES associated with ANALGESICS TYPE AND DOSES					
Non Narcotic Medications		**Narcotic Medications**			
1 POINT		**4 POINTS**			
Any route		**Oral/Rectal**		**IV/IM/SC**	
Generic Name	**Dose (mg)**	**Generic Name**	**Dose (mg)**	**Generic Name**	**Dose (mg)**
Aceclofenac	100	Anileridine	25		
Acemetacin	90	Buprenorphine	0.8	Buprenorphine	0.8
Acetaminophen / Paracetamol	325			Butorphanol	1
Aminophenazone	500	Codeine	60		
Aspirin	325	Dextropropoxyphene	50		
Celecoxib	100	Dihydrocodeine	30		
Diclofenac	25	Fentanyl*	100 µg	Fentanyl*	50 µg
Diflunisal	250	Hydrocodone	10	Hydrocodone	5
Dipyrone/ Metamizole	500	Hydromorphone	2	Hydromorphone	1
Etodolac	200	Levorphanol	2	Levorphanol	2
Fenoprofen	200	Meperidine/ Pethidine	100	Meperidine/ Pethidine	50
Flurbiprofen	50	Methadone	10		
Ibuprofen	200	Morphine	10	Morphine	5
Indomethacin	25	Oxycodone	5	Oxycodone	2.5
Ketoprofen	25	Oxymorphone rectal	2.5		
Ketorolac	10			Papaveretum	15.4
Mefenamic Acid	250	Pentazocine	50	Pentazocine	30
Nabumetone	500	Piritramide	15		
Naproxen	250	Propoxyphene	50		
Nefopam	20	Tilidine	50		
Nimesulide	100	Tramadol	50	Tramadol	50
Piroxicam	10				
Propyphenazone	250				
Rofecoxib	12.5				
Tenoxicam	20	* Fentanyl patch (TTS): 36 points / day for 25µg/hour patch			

9.6 Other Assessments (One Year Post-Randomisation Date)

Dual energy X-ray absorption (DXA) scan, bone density scan (1 year post-randomisation date only, +/- 3 months)

The DXA scan is only required if the participating centre is participating in the Bone Density sub-study.

9.7 Flow Chart of Trapeze Study Procedures and Assessments

Investigations	Pre-randomisation	On Treatment Primary Treatment Period (cycles 1 – 6)	Post-primary treatment period (cycles 1 - 6) assessment	Follow-up
1. Informed consent	✓			
2. History / physical exam (including clinical tumour assessment and new skeletal events)	Within 28 days	Every 3 weeks (prior to docetaxel infusion)	Cycle 6 (Day 21) Before Sr89 infusion or subsequent treatments	Clinical tumour assessment: Every 3 months
3. Haematology [1] & clinical chemistry tests [2]	Within 28 days	Every 3 weeks (prior to docetaxel infusion)	Cycle 6 (Day 21) Before Sr89 infusion or subsequent treatments	Every month for the first 3 months, then every 3 months until study completion or patient withdrawal
4. Serum Creatinine	Within 28 days	Every 3 weeks throughout treatment, prior to each infusion	Cycle 6 (Day 21) Before Sr89 infusion or subsequent treatments	-
5. PSA [3]	Within 28 days	Every 3 weeks (day 1 before infusion)	Cycle 6 (Day 21) Before Sr89 infusion or subsequent treatments	At each follow-up assessment until disease progression
6. Adverse events reporting / collection [4]	Within 28 days	AEs logged for all treatment period	-	Until 60 days after the last study drug administration
7. *Radiology tumour assessment (CT scan/ chest x-ray/ bone scan)	Recommend within 56 days	As clinically indicated	If disease progression suspected, clinically or biochemically	If disease progression suspected, clinically or biochemically
8. CT scan or chest x-ray **	Within 28 days	As clinically indicated	As clinically indicated	As clinically indicated
9. DXA bone density scan	Within 28 days	-	-	1 year from randomisation date
10. Quality of life & Health economics[5]	Within 3 days	Every 3 weeks (prior to docetaxel infusion)	Cycle 6 (Day 21) Before SR89 infusion or subsequent treatments	Every visit (until study completion or patient withdrawal)
Pain assessments: PPI + Analgesic Score	Within 3 days, averaged over 7 days	Every 3 weeks (prior to docetaxel infusion) averaged over 7 days	Cycle 6 (Day 21) Before SR89 infusion or subsequent treatments	Every visit (until study completion or patient withdrawal)
Proteomic blood sample	Within 28 Days	Every 2 Cycles Cycle 2,4,6	Every 2 cycles Cycle 8, 10 and end of treatment	-

[1] WBC, neutrophils, platelet, haemoglobin
[2] Urea, serum creatinine, potassium, sodium, calcium, magnesium, AST ALT, alkaline phosphatase, total bilirubin, blood glucose
[3] Refer to inclusion criteria section 5 for rising and elevated PSA assessments
[4] Refer to section 11 for specific adverse event reporting.
[5] Self administered EuroQol & Fact-P questionnaire, plus health problems questionnaire for health economics. QoL questionnaire should be administered before randomization or at randomization, but in any case before the patient is informed of the treatment to which he is assigned
* To ensure comparability, the baseline X-rays/ultrasounds/scans and subsequent X-rays/ultrasounds/scans to assess response must be performed using identical techniques (i.e., scans performed immediately following bolus contrast administration using a standard volume of contrast, the identical contrast agent, and preferably the same scanner). Each lesion must be followed with the same method throughout the study (from baseline until follow-up).
** To be performed at baseline:

10 MEASUREMENT OF OUTCOME

Table 10.1: Measurement of Outcome

Phase	Primary	Subsidiary	Ancillary measures and exploratory outcomes
II	• Feasibility, tolerability and safety in terms of cycles of docetaxel, prednisolone, zoledronic acid and Sr89 received, cycle delays, dose reductions and toxicity	• Clinical progression-free survival • Skeletal-related-event-free survival • Pain progression-free survival • Overall survival • Costs • Quality of life	• Changes in bone mineral density (sub-study) • Biological profiling for prognostic and predictive indicators (sub-study) • PSA-related outcomes • Patient-reported pain-related outcomes
III	• Clinical progression-free survival • Costs and cost-effectiveness	• Skeletal-related-event-free survival • Pain progression-free survival • Overall survival • Quality of life • Toxicity	• Changes in bone mineral density (sub-study) • Biological profiling for prognostic and predictive indicators (sub-study) • PSA-related outcomes • RECIST criteria-related outcomes • Patient-reported pain-related outcomes

10.1 Primary Outcome Measures

10.1.1 Phase II primary outcomes: feasibility, tolerability and safety

The primary outcomes for the phase II analysis are feasibility, tolerability and safety, and will be measured in terms of:

Treatment Received

- Mean number of cycles of docetaxel received per patient and the proportion of patients receiving 6 cycles.
- Mean number of cycles of zoledronic acid received per patient and the proportion of patients receiving 6 cycles.
- The proportion of patients who receive Sr89 after receiving 6 cycles of chemotherapy.

Dose Delays and Reductions

- Mean number of cycles of docetaxel per patient with dose delay, and proportion of patients who experience at least one dose delay.
- Mean number of cycles of docetaxel per patient with dose reduction and proportion of patients who experience at least one dose reduction.

Adverse Events

- Proportion of patients with at least one grade 3 or 4 adverse event.
- Proportion of patients experiencing at least one grade 3 or 4 adverse event for specific categories of toxicity, i.e. infection, musculoskeletal or haematological.

Serious Adverse Events (SAEs)

- Mean number of SAEs per patient, and proportion of patients with at least one SAE.
- Proportion of patients with at least one Serious Adverse Reaction (SAR).
- Proportion of patients with at least one Suspected Unexpected Serious Adverse Reaction (SUSAR).

10.1.2 Phase III primary outcome: clinical progression-free survival

The primary outcome for the phase III analysis is clinical progression-free survival (CPFS). CPFS time is defined as the time, in whole number of days, between the date of randomisation and the date of clinical progression. Clinical progression is defined as the earliest of the:

- date of occurrence of pain progression;
- date of occurrence of a skeletal-related event, if disease related;
- date of death from any cause.

CPFS is a composite endpoint with three component events in the definition, the occurrence of any one of which means that the patient has reached clinical progression and must therefore be withdrawn from *all* trial treatments. For patients who are withdrawn from the study or lost to follow-up, CPFS time will be censored at the date they were last known to be alive. For those patients who do not experience at least one of these component events during the course of the trial, CPFS time will be censored at their last follow-up date.

Pain Progression

Pain progression is defined as clinical evidence of an increase in pain which, in the opinion of the treating clinician, is sufficient to warrant discontinuation of trial treatments and to trigger a change in therapy (e.g. to radiotherapy). The date of pain progression is defined as the date on which the decision to discontinue trial treatment is made.

NOTE: Prior to baseline, on the development of pain in an area, which involves a new area of the skeleton not present at baseline (randomisation into the clinical trial), we recommend that a radiological assessment of the bone should be performed (via CT scan, MRI, plain X-ray or bone scan) to assess if there is bone disease progression.

Skeletal-Related Event (SREs)

Any given patient may experience more than one occurrence of an SRE. **All** SREs must be recorded, but the date of occurrence of the earliest SRE must be used for the purposes of determining the date of clinical progression. Each of the following events constitute an SRE:

- Symptomatic pathologic bone fractures
- spinal cord or nerve root compression likely to be related to cancer or to treatment
- cancer-related surgery to bone (includes procedures to set, or stabilise, pathologic fractures or areas of spinal cord compression and procedures to prevent imminent fracture or spinal cord compression)
- radiation therapy to bone (including the use of radioisotopes)
- change of anti-neoplastic therapy to treat bone pain due to prostate cancer
- Hypercalcaemia
- Initiation of bisphosphonate therapy in response to new bone pain symptoms

Death

Death from any cause will be included as an event.

10.1.3 Phase III Primary Outcome: Health Economics Outcomes

One of the primary objectives of the trial is to compare treatment arms in terms of costs and cost-effectiveness. The economic analysis will be carried out from UK NHS and social service perspectives. Key resource-use data will be collected; by the CRF and supplemented by patient-completed resource use questionnaires. This will include primary care consultations, medication and use of secondary care services (outpatient visits, A&E visits and, inpatient hospital stays). The itemized use of each resource will be weighted by its unit cost to give the aggregate cost per patient. Unit costs will be obtained from NHS reference costs and relevant routine sources – PSSRU (Curtis and Netten, 2006). QoL will be assessed using the EQ-5D questionnaire. A utility score will be generated from this questionnaire. QALYs will be calculated. A cost-effectiveness analysis will be conducted in which outcome will be measured as incremental cost per-QALY gained within the trial.

10.2 Subsidiary Outcomes

10.2.1 Skeletal Related Event-Free Interval (SREFI)

SREs are defined in the section describing clinical progression-free survival. The skeletal related event-free interval (SREFI) is defined as the time in whole number of days between the date of randomisation and the date of the first skeletal related event. For patients who do not experience a skeletal related event, SREFI will be censored at either the date of death, date of last follow up or date withdrawn consent, whichever is earliest..

10.2.2 Pain Progression-Free Interval (PPFI)

Pain progression is defined in the section describing clinical progression-free survival. Pain progression-free interval (PPFI) is defined as the time in whole number of days between the date of randomisation and the date of pain progression. For those patients who do not experience pain progression, PPFI will be censored at either the date of death, date of last follow up or date withdrawn consent, whichever is earliest.

10.2.3 Overall survival

Overall survival time is the time in whole number of days between the date of randomisation and the date of death, from any cause. For patients who are withdrawn from the study or who are lost to follow-up, survival time will be censored at the date they were last known to be alive. For patients who do not die during the course of the study, survival time will be censored on the date they were last known to be alive.

10.2.4 Quality of life

QoL will be assessed using the EQ-5D and FACT-P and Health Problems questionnaires, which are patient completed questionnaires (see appendix 3). The EQ-5D is a generic utility-based measure of health-related QoL that has been widely used in economic analyses of healthcare interventions. It is being used in this trial in order that improvements in overall QoL can be estimated and measured in terms of the strength of preference for such improvements. The instrument is designed to be self-completed and so, where possible, the patient will provide the data. Patients will also be asked to complete pain diary sheets and QoL questionnaire booklets, which include the EQ-5D, FACT-P, and study-specific heath-related questionnaires, during their treatment (see appendices 3-5).

10.2.5 Toxicity of treatment

Toxicity of treatment will be measured in terms of the occurrence, severity, type and causality of adverse events during the treatment period.

10.3 Outcomes from Ancillary Biomarker Studies

10.3.1 Bone mineral density changes

Changes in bone density will be monitored by a DXA scan. These scans will be done at baseline (within 28 days of randomisation) and at 1 year following the date of randomisation. The results of these scans will be analysed along with the recording of any disease in the region of bone density measurements. The regions of the skeleton used for the bone density measurement will be the right or left-forearm (non-dominant arm) as well measurements at spine, hip and neck of femur if unaffected by metastases. Patient participation in this part of the study will be voluntary; declining to participate will not prevent entry into the main study.

10.3.2 Biological profiling for prognostic and predictive indicators

Blood (serum) samples will be taken at regular intervals during the treatment phase of the study, i.e. baseline and end of treatment cycles 2, 4, 6, 8 and 10. Patient consent for the collection of these samples will be recorded on the patient consent form. Patient participation in this part of the study will be voluntary; declining to participate will not prevent entry into the main study.

In addition to blood samples, archived diagnostic or other subsequent tissue biopsies from the prostate or metastatic sites (paraffin fixed and embedded tissue blocks) from a proportion of patients will be collected, subject to patient consent. These samples will subsequently be sent to the Trapeze co-ordinating centre by individual participating centres. This collection of tissue blocks will only occur subject to adequate funding arrangements. It is proposed that the collection of these samples will take place towards the end of the recruitment phase of the trial. These samples will then be subject to biological profiling of prognostic and predictive indicators. This information will then be collated with the clinical data derived from the trial.

10.4 Exploratory Outcomes

Exploratory outcomes will not be used to directly evaluate the treatments being compared in this trial, but rather to investigate the extent to which they are associated with other outcomes.

10.4.1 Patient-reported pain events

The primary analysis of differences in pain-related outcomes between treatment arms will be based on clinician-reported pain (see section 10.1.2). However, further exploratory analyses will also be undertaken using the patient-reported pain data recorded in pain diaries (see section 9.1.4), including measures of pain response and patient-reported pain progression.

10.4.2 PSA-related events

PSA will be measured at every study assessment and protocol-defined patient visit. Exploratory analyses of several conventional PSA-related events will be undertaken.

10.4.3 Number of SREs

The number of SREs is defined as the number of SREs occurring between the date of randomisation and the earliest of: the date of death; and the date of the end of follow-up.

10.4.4 RECIST criteria-related events

Patients will be evaluated with respect to RECIST (version 1.0) criteria, as appropriate (see Appendix 2). Exploratory analyses of several conventional RECIST criteria related events will be undertaken.

11 SAFETY ASSESSMENT

11.1 Definitions

11.1.1 Adverse event

An Adverse Event (AE) is defined as any untoward medical occurrence in a patient or clinical trial subject administered either docetaxel, prednisolone, zoledronic acid or Sr89, either administered alone or in combination, and which does not necessarily have a causal relationship with this treatment.

Comment: An AE can therefore be any unfavourable and unintended sign (including abnormal laboratory findings), symptom or disease temporally associated with the use of an IMP, whether or not considered related to the IMP.

11.1.2 Adverse reaction

An Adverse Reaction (AR) is defined as all untoward and unintended responses to a study drug related to any dose administered.

Comment*:* An AE judged by either the reporting Investigator or Sponsor as having a causal relationship to the IMP qualifies as an AR. The expression causal relationship means to convey in general that there is evidence or argument to suggest a causal relationship.

11.1.3 Unexpected adverse reaction

An Unexpected Adverse Reaction (UAR) is defined as an AR, the nature or severity of which is not consistent with the applicable with the current product information. The Summary of manufacturer's Product Characteristics (SmPC) for each of the study drugs (docetaxel, zoledronic acid, prednisolone and Sr89) will be used to assess each AE reported as part of a SAE.

Comment: When the outcome of an AR is not consistent with the applicable product information, the AR should be considered unexpected.

Severity: The term "severe" is often used to describe the intensity of a specific event. This is not the same as "serious", which is based on patients/event outcome or action criteria.

11.1.4 Serious adverse event or serious adverse reaction

A Serious Adverse Event (SAE) or Serious Adverse Reaction (SAR) is defined as any untoward medical occurrence or affect that at any dose:

- Results in death
- Is life-threatening[1]

- Requires inpatient hospitalisation[2] or prolongation of existing hospitalisation
- Results in persistent or significant disability or incapacity
- Is a congenital anomaly/birth defect[3]

Comment: Medical judgment should be exercised in deciding whether an AE or AR is serious in other situations. An AE or AR that is not immediately life-threatening or does not result in death or hospitalisation but may jeopardise the subject in some way or may require intervention to prevent one of the other outcomes listed in the definition above, should be considered serious.

[1] Life-threatening in the definition of an SAE or SAR refers to an event in which the patient was at risk of death at the time of the event; it does not refer to an event that hypothetically might have caused death if it were more severe.

[2] Hospitalisation is defined as an inpatient admission, regardless of length of stay, even if the hospitalisation is a precautionary measure for continued observation.

[3] This will include children of fathers receiving study therapy

11.1.5 Suspected unexpected serious adverse reactions

A Suspected Unexpected Serious Adverse Reaction (SUSAR) is defined as a SAR that is unexpected, i.e. the nature, or severity, of the event is not consistent with the applicable summary of product information (SmPC).

A SUSAR should meet the definition of an AR, UAR and SAR as detailed above.

11.1.6 List of expected adverse reactions (SARs)

For a list of all expected adverse reactions please refer to the relevant SmPC.

11.1.7 SAEs that do not require reporting for Trapeze

The following reasons for hospitalisation do not require reporting as SAEs for Trapeze unless associated with other serious advents:

- Admissions for study therapy;
- Admissions for procedures related to the patient's disease (e.g. placement of an indwelling catheter or a planned admission for a blood transfusion for low haemoglobin levels only).

11.1.8 Reporting period

Details of all SAEs must be documented from the date of consent until 60 days after the last administration of study drug. Patients must be followed-up until resolution of the SAE.

NB: Zoledronic acid will be considered a study drug only if the drug was assigned during the randomisation process (Arms B and D). If zoledronic acid is prescribed AFTER the patient has progressed, as defined by section 8.5.2, the drug will no longer be considered a study drug and will not be subject to the SAE reporting procedures. In such a case zoledronic acid administrations should be recorded on the Concomitant Medications Running Log.

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There is no time limit for reporting SAEs thought by the Investigator to meet the definition of a post-study SUSAR.

11.2 Assessment of Adverse Events

All adverse events (AEs) will be collected for patients with TNOs below 300. For those with TNOs above 300 grades 3 and 4 will be will be collected. All AEs must be graded according to the NCI CTCAE Toxicity Criteria (Version 3).

For adverse events not listed in the toxicity table, severity should be recorded as:

Mild	does not interfere with subject's usual functioning
Moderate	interferes to some extent with subject's usual functioning
Severe	interferes significantly with subject's usual functioning

Life-threatening risk of death, organ damage or disability

Relationship to study therapy will be assessed using the following definitions:

Unrelated	There is no evidence of any causal relationship.
Unlikely to be related	There is little evidence to suggest there is a causal relationship (e.g. the event did not occur within a reasonable time after administration of the trial medication). There is another reasonable explanation for the event (e.g. the patient's clinical condition, other concomitant event).
Possibly related	There is some evidence to suggest a causal relationship, e.g. the event occurred within what the treating clinician felt was a reasonable period following administration of the trial medication. However, the influence of other factors may have contributed to the event, e.g. the patient's clinical condition, other concomitant events.
Probably related	There is evidence to suggest a causal relationship, and the influence of other factors is unlikely.
Definitely related	There is clear evidence to suggest a causal relationship, and other possible contributing factors can be ruled out.

NOTE: All adverse events considered to be "possibly related", "probably related", or "definitely related" will be reported as a SAR or SUSAR in all Trapeze-related safety reports. In line with MHRA guidance and CRCTU practice, "unlikely to be related" events will not be reported as SARs or SUSARs.

11.3 Reporting of Adverse and Serious Adverse Events

11.3.1 Adverse events

Adverse Events must be recorded on the Adverse Event Running Log of the CRF, including date of onset, severity, duration and relationship to study therapy, whether on-going and stop date. AEs which are also SREs must also be recorded on an SRE CRF.

If more than one AE occurs, each one must be recorded separately. The Investigator should take all therapeutic measures necessary for resolution of any AE. Any medication necessary for the treatment of an AE must be recorded on the patient's Concomitant Medication Running Log.

11.3.2 Serious adverse events

In the case of an SAE the Investigator must immediately:

Complete a SAE Form – the form can be completed and signed by a member of the site trial-team who has been delegated this responsibility by the Investigator, but should be checked and counter signed by the local Investigator at a later date.

Send the original SAE form with fax coversheet to the Trials Office once signed by the Investigator;
Report SAE in accordance with local institutional policy:

Fax form to [redacted] (or [redacted], if primary number is unobtainable)

Continue follow-up of the subject until clinical recovery is complete or any sequelae have stabilised;
Provide follow-up information on a SAE Form on resolution of the event;

On receipt of a SAE CRF, seriousness and causality of the event will be determined independently by a Clinical Co-ordinator. An SAE judged by either the local investigator or Clinical Co-ordinator, or both, to have a reasonable causal relationship with the trial medication will be regarded as a SAR. The Clinical Co-ordinator will also assess all SARs for expectedness. If the event meets the definition of a SAR that is unexpected in nature it will be classified as a SUSAR.

11.4 Reporting of Events to Other Organisations

11.4.1 Regulatory authorities and main research ethics committee

SUSARs

The Trials Office will report a minimal data set of all individual events categorised as a fatal or life-threatening SUSAR, to the Medicines and Healthcare products Agency (MHRA) and main Research Ethics Committee (MREC) within seven days. Detailed follow-up information will be provided within an additional eight days. All other events categorised as SUSARs will be reported within 15 days.

SARs

The Trials Office will report details of all SARs (including SUSARs) to the MHRA and MREC annually, from the date of the Clinical Trial Authorisation, in the form of an Annual Safety Report.

AEs

Details of all reported AEs experienced during chemotherapy (i.e. grades 1-4 for patients 1-300; grades 3-4 for patients 301+) will be reported to the MHRA on request.

Other Safety Issues Identified During the Course of the Trial

The MHRA and main REC will be notified immediately if a significant safety issue is identified during the course of the trial.

11.4.2 Investigators

Details of all SUSARs and any other safety issue which arises during the course of the trial will be reported to all Trapeze Investigators.

11.4.3 Independent data monitoring committee

An Independent Data Monitoring Committee will review all SAEs annually.

11.4.4 Novartis Oncology, Sanofi-Aventis and GE Healthcare

All SAEs classified as “unlikely to be related”, “possibly related”, “probably related” or “definitely related” to docetaxel, zoledronic acid and Sr89, must be reported to Sanofi-Aventis, Novartis Pharmaceuticals (UK) Ltd, or GE Healthcare, respectively, within 24 hours by fax.

12 STATISTICAL CONSIDERATIONS

12.1 Study Analysis

The definitive study analysis will be conducted on an intention-to-treat basis. All tests of statistical significance will be conducted at the 5% two-sided significance level. The phase II analysis will compare all four treatment arms with respect to feasibility, tolerability and safety whereas the phase III analysis will assess treatments with respect to efficacy within a 2x2 factorial design framework, i.e. the trial will compare (i) ZA versus no ZA (stratified for Sr89 use) and (ii) Sr89 versus no Sr89 (stratified for ZA use).

12.1.1 Analysis of outcome measures

Feasibility, tolerability and safety. In the primary phase II analysis, the feasibility, tolerability and safety of each treatment arm will be reported in terms of the measures specified in section 10.1.1. The analysis will be purely descriptive and the data on the control arm will act as a benchmark against which to assess the experimental treatment arms. Proportions and means will be calculated, and 95% confidence intervals constructed as appropriate.

Clinical progression free survival (CPFS). The primary phase III analysis will compare ZA versus no ZA (stratified for Sr89 use) and Sr89 versus no Sr89 (stratified for ZA use) in terms of CPFS. Treatments will be compared using the Kaplan-Meier method and a log-rank test. Statistical models for time-to event data that account for other factors which are potentially related to outcome, in addition to treatment, will also be used. In particular, Cox regression models will be considered, and the possibility of fitting parametric survival models investigated. Time-to-event will be measured between date of randomisation and date of first detection of the event, with censoring dealt with appropriately (see section 10).

Overall survival. The approach adopted for the analysis of clinical progression-free survival time will also be used to analyse overall survival time.

Pain-progression-free survival. The approach adopted for the analysis of clinical progression-free survival time will also be used to analyse pain-progression-free survival time.

Skeletal-related event-free survival. The approach adopted for the analysis of clinical progression-free survival time will also be used to analyse skeletal-related event-free survival time.

Quality of life. Quality of life data will be analysed using longitudinal statistical methods and consideration will be given to missing data that occurs due to dropout and death. The balance between quality of life and survival will be analysed by comparing treatments in a quality-adjusted survival analysis[28].[25]

Health economic analysis. The cost-effectiveness of treatments will be evaluated primarily by balancing the healthcare costs on each of the treatment arms during clinical progression-free survival time against the measure of clinical effectiveness. In addition cost-effectiveness (cost-per-life-year gained) and cost-utility (cost-per-quality-adjusted life-year) analyses will be undertaken. Both probabilistic and univariate sensitivity analyses will be performed, with results reported using both cost-effectiveness planes and cost-effectiveness acceptability curves (plot of CE thresholds against the probability that the intervention is cost-effective). Given the planned long-term follow-up of patients in the trial, lifetime costs and effects will largely be observed and so it is not envisaged that extrapolation beyond the trial will be required.

The mean difference in costs across treatment arms and the associated 95% confidence interval will be estimated using non-parametric bootstrapping to account for the expected skewed distribution of the cost data. An incremental cost-effectiveness analysis will be conducted. The base-case analysis will be framed in terms of cost-consequences, reporting data in a disaggregated manner on the incremental cost and the important consequences (including data on quality of life, etc.). If this identifies a situation of dominance then further analysis will not be required. If no dominance is found then cost-effectiveness analyses (i.e. cost-per-clinical progression-free life-year and cost-per-life-year) and cost-utility analysis (i.e. cost-per-quality-adjusted life-year) will be employed. Quality-adjusted life-years (QALYs) will be calculated using EQ-5D data collected as part of the trial. The results of the economic analyses will be presented using cost-effectiveness acceptability curves to reflect sampling variation and uncertainties in the appropriate threshold cost-effectiveness value. We will also use both simple and probabilistic sensitivity analyses to explore the robustness of these results to plausible variations in key assumptions and variations in the analytical methods used, and to consider the broader issue of the ability to generalise the results.

Toxicity. The analysis of toxicity will be purely descriptive. Proportions and means will be calculated, and 95% confidence intervals constructed as appropriate.

Measures from ancillary biomarker studies. The analysis of changes in bone mineral density will be exploratory and entirely descriptive, with summary statistics and their associated 95% confidence intervals constructed as appropriate. It is anticipated that the same approach will be adopted for the analysis of prognostic and predictive indicators, but this will be re-examined prior to seeking separate funding for these sub-studies.

Exploratory outcomes. The analysis of patient-reported pain outcomes, PSA-related outcomes, and RECIST criteria-related outcomes which can be considered time-to-event data will be analysed using the approach adopted for the analysis of clinical progression-free survival; outcomes which can be treated as repeated measurements will be analysed using methods suitable for longitudinal data. Number of skeletal-related events will be analysed using methods appropriate to count data.

12.2 SAMPLE SIZE

12.2.1 Phase II

The analysis of the phase II component of the trial will be entirely descriptive and will not involve any statistical hypothesis testing. The primary outcomes are feasibility, tolerability and safety and these will be measured as proportions or means, as appropriate: recruitment of 50 patients into each arm will ensure that proportions are estimated with a precision of at least 15%, and provide sufficient data to be able to assess the arms in terms of their suitability for progression into the phase III component of the trial.

12.2.2 Phase III

Sample size calculations are based on the primary outcome measure of clinical progression-free survival time (CPFS). The calculations are the same for both the comparison of ZA versus no ZA and Sr89 compared to no Sr89. The trial aims to detect a hazard ratio of 0.76 (equivalent to 1 year CPFS rates of 30% vs 40%, assuming CPFS follows an exponential distribution). The number of *events* required to detect this difference in each group for either treatment comparison, using a two-sided 5% significance level and 80% power, is 206; it is estimated that approximately 294 patients per arm i.e. 588 patients in total will need to be recruited to observe this number of events. We will aim to recruit a minimum of 618 evaluable patients, which allows for 5% dropout.

12.2.3 Timing of analyses

Interim analysis will be carried out at least once a year for consideration by the independent Data Monitoring Committee (DMC), and more often if required. Final analysis of the phase II data wasl presented to the DMC after 200 patients were recruited and followed-up for at least seven months, and all relevant data returned to the trial office. At this point the IDMC determined that the trial should continue into phase III. Final analysis of the phase III trial will take place once all patients have been followed up for one year, and all patients have complete data.

12.4 Milestones

The target recruitment rate is 15 to 25 patients per month, from a total of up to 50 centres. It is anticipated that 618 evaluable patients will have been recruited by the end of the first quarter of 2012.

The milestones below are guidelines based on predicted future recruitment rates, as well as dates of real events which occurred prior to the preparation of this version of the protocol.

Dec 2004	Start randomisation
Sept 2006	First Report to DMC
Dec 2007	Second Annual DMC meeting to review safety data and recruitment
July 2008	DMC Meeting to review safety data and recruitment
Oct 2008	TSC Meeting to review clinical trial, DMC recommendations and recruitment
Nov 2008	Accrual of 300 patients reached
Feb 2009	DMC Meeting to review safety data
May 2009	Determination of Phase III protocol treatment arms and study numbers (if required: a protocol amendment to be submitted to Ethics and MHRA for approval). The Milestones after this date to be determined by the exact finalised protocol details.
Sept 2010	DMC Meeting to review safety data and recruitment
Oct 2010	TSC Meeting to review clinical trial, DMC recommendations and recruitment
June 2011	DMC Meeting to review requested further data
Jan 2012	DMC Meeting to review requested further safety and SRE data
Mar 2012	TSC Meeting to review clinical trial, DMC recommendations and recruitment
End Feb 2012	Trial closing to recruitment

13 TRIAL COMMITTEES

13.1 Trial Management Group

The Trial Management Group (TMG) is comprised of the Chief Investigator, other co-investigators and members of the CRCTU as detailed in the front sleeve of the protocol. The TMG will be responsible for the day-to-day running and management of the trial and will meet by teleconference, or in person, as required. See Figure 1 for the relationship between all committees.

13.2 Trial Steering Committee

An independent Trial Steering Committee (TSC) will provide overall supervision for the trial and provide advice to the TMG. Membership includes the Chief Investigator or his deputy, and an independent oncologist, urologist and statistician. The ultimate decision regarding continuation of the trial lies with the TSC. The TSC will meet at least once a year or more often if required.

13.3 Independent Data Monitoring Committee

An Independent Data Monitoring Committee (DMC) has been established for this study. The DMC will be the only group who see the confidential reports on the data accumulating to the trial. Their main objective will be to advise the TSC as to whether there is any evidence or reason as to why the study should be amended or terminated based on the recruitment rate or safety. Reports to the DMC will be produced by the CRCTU. The first meeting of the DMC occurred when 121 patients had been randomised into the trial. Thereafter, the DMC will meet at intervals determined by the DMC (at least every year), to monitor recruitment to the trial, protocol compliance, toxicity, and serious adverse events. The DMC may consider discontinuing the trial if the recruitment rate or data quality are unacceptable, or if there are cases of excessive toxicity. The DMC would also stop the trial early if the interim analyses showed differences between treatments, which, in their opinion, were deemed to be convincing to the clinical community. Further details of DMC functions and the procedures for interim analysis and monitoring are provided in the DMC charter (available on request).

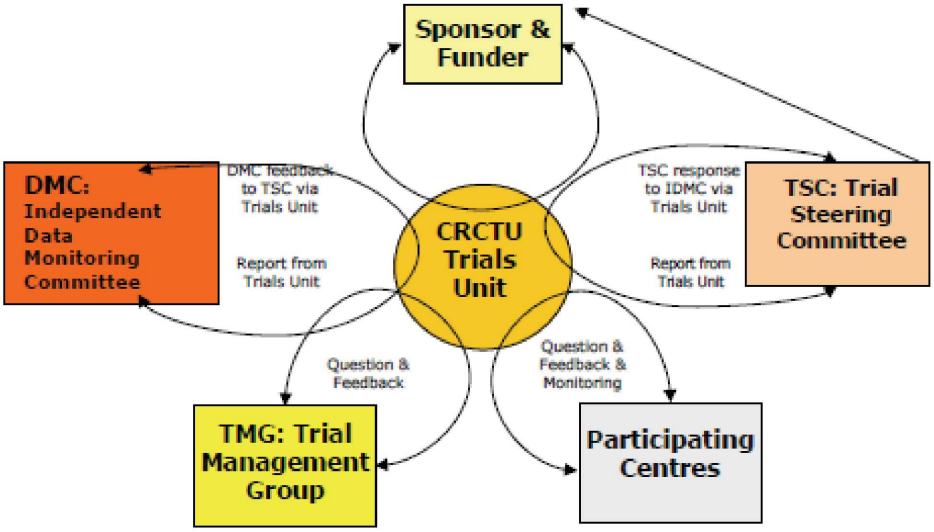

Figure 2: Diagram of the Relationship between Committees and the CRCTU Trials Unit

14 REGULATORY & ETHICS COMMITTEE (EC) APPROVAL

14.1 Ethical Considerations

This study will be carried out in accordance with the World Medical Association (WMA) Declaration of Helsinki (1964) and the Tokyo (1975), Venice (1983), Hong Kong (1989), South Africa (1996) and Scotland (2000) amendments. Copies of the declaration may be obtained by contacting the Trapeze Study Office, or directly from the WMA website at http//www.wma.net/e/policy/17-c_e.html.

The protocol has gained ethical approval from the South West MREC. Before entering patients into the study, the Principal Investigator must ensure that the protocol has approval from their local Research Ethics Committee and local Research and Development (R&D) Office.

14.2 Informed Consent

It is the responsibility of the investigator to obtain written informed consent from each patient prior to entering the trial, in compliance with national requirements.

14.3 Patient Confidentiality

The personal data recorded on all documents will be regarded as strictly confidential. To preserve the patient's anonymity, only their initials, date of birth, and hospital number will be recorded on the case report forms. With the patient's permission, their name will be collected at randomisation to allow flagging with the Office of National Statistics. The Principle Investigator must ensure the patient's anonymity is maintained. The Investigator must maintain documents which are not intended for submission to the trials office in strict confidence.

The trials office will maintain the confidentiality of all patient data and will not reproduce or disclose any information by which patients could be identified. Patients must be reassured that their confidentiality will be respected at all times.

In the case of special problems and/or governmental queries, it will be necessary to have access to the complete study records, provided that patient confidentiality is protected.

15 INDEMNITY & INSURANCE

This study is a clinician-initiated and clinician-led study with education grants provided by Sanofi-Aventis and Novartis Pharmaceuticals (UK) Ltd. In addition a Health Technology Assessment (HTA) programme grant was approved in December 2006. This grant was activated in April 2007 and will provide funding for the study until 2013. The study is being run by the Cancer Research UK Clinical Trials Unit (CRCTU), School of Cancer Sciences (Formerly Institute for Cancer Studies), The University of Birmingham. The University of Birmingham will act as the sponsor for the study. As sponsor, the University is responsible for the general conduct of the study and shall indemnify the Investigation Centre against any claims arising from any negligent act or omission by the University in fulfilling the Sponsor role in respect of the Study. The University is under no obligation to indemnify the Investigation Centre against any claims arising from the conduct of the Study at the Centre.

In terms of liability, NHS Trust and Non-Trust Hospitals have a duty of care to patients treated by them, whether or not the patient is taking part in a clinical trial. Compensation is therefore only available in the event of clinical negligence being proven. There are no specific arrangements for compensation made in respect of any serious adverse events occurring though participation in the study, whether from the side-effects listed, or others as yet unforeseen.

Novartis Pharmaceuticals (UK), Sanofi-Aventis, and GE Healthcare Ltd are liable, on a no fault basis, for the quality and fitness-for-use of their products.

16 PUBLICATION POLICY

The main trial results will be published in the name of the trial in a peer-reviewed journal, on behalf of all collaborators. The manuscript will be prepared by a writing group, appointed from amongst the Trapeze Trial Steering Committee, Trial Management Group and high-accruing Investigators. The CRCTU and all participating centres and Investigators will be acknowledged in this publication. All presentations and publications relating to the trial must be authorised by the Trapeze Trial Steering Committee.

17 STUDY COSTS AND RELATIONSHIP WITH PHARMACEUTICAL INDUSTRY

Sanofi-Aventis and Novartis provided an educational grant to CRCTU, CRUK, School of Cancer Sciences (formerly the Institute for Cancer Studies), University of Birmingham, to conduct the study (first 300 patients only). Subsequently, a grant from the Health Technology Assessment (HTA) programme was secured in December 2006 to provide funding and support for the expansion of the initial programme into a Phase III clinical trial. This funding is secured until April 2013 (subject to conditions).

Sanofi-Aventis and Novartis Pharmaceuticals (UK) Ltd also provided study drugs (Taxotere® (docetaxel) and Zometa® (zoledronic acid), respectively) free-of-charge for the first 300 patients recruited into the trial. Docetaxel is now NICE approved and therefore funding is nationally endorsed for this medicine for mHRPC patients. From patient 301 onwards docetaxel will be purchased by individual hospitals at local hospital prices. Sanofi-Aventis continued to support the clinical trial with a £300 grant (paid to the national co-ordinating centre) for patients recruited into the trial with trial numbers 301 to 700.

For patients 301 and above, the following other arrangements will apply:

Zoledronic acid (Zometa®) will be supplied to participating centres with a 28.2% discount on the standard NHS list price. This means that each 4mg vial will cost £140.

GE Healthcare Limited have extended their trial discount (5%) Metastron® (Sr89), for patients entered into Trapeze to receive a single administration of Metastron®, for the period 1 September 2011 until 31 October 2012.

The trial data, including quality of life information, the health economic study and pathological material collected as part of the biological studies, will remain the property of the Trial Management Group.

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PROTOCOL APPENDIX 1: ECOG PERFORMANCE STATUS SCALES

ECOG Performance Status

These scales and criteria are used by doctors and researchers to assess how a patient's disease is progressing, assess how the disease affects the daily living abilities of the patient, and to determine appropriate treatment and prognosis. They are included here for health care professionals to access.

ECOG PERFORMANCE STATUS*

Grade	ECOG
0	Fully active, able to carry on all pre-disease performance without restriction
1	Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, e.g., light house work, office work
2	Ambulatory and capable of all self-care but unable to carry-out any work activities. Up-and-about for more than 50% of waking hours
3	Capable of only limited self-care, confined to bed or chair for more than 50% of waking hours
4	Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair
5	Dead

* As published in Am. J. Clin. Oncol.:

Oken, M.M., Creech, R.H., Tormey, D.C., Horton, J., Davis, T.E., McFadden, E.T., Carbone, P.P.: Toxicity And Response Criteria Of The Eastern Cooperative Oncology Group. Am J Clin Oncol 5:649-655, 1982

PROTOCOL APPENDIX 2 ; RESPONSE EVALUATION CRITERIA IN SOLID TUMOURS

1.0 Definition of Measurable and Non-Measurable Lesions.

Measurable disease - the presence of at least one measurable lesion. If the measurable disease is restricted to a solitary lesion, its neoplastic nature should be confirmed by cytology/histology.

Measurable lesions - lesions that can be accurately measured in at least one-dimension with longest diameter ≥20 mm using conventional techniques or ≥10 mm with spiral CT scan.

Non-measurable lesions - all other lesions, including small lesions (longest diameter <20 mm with conventional techniques or <10 mm with spiral CT scan), i.e. leptomeningeal disease, ascites, pleural/pericardial effusion, inflammatory breast disease, lymphangitis cutis/pulmonis, cystic lesions, and also abdominal masses that are not confirmed and followed by imaging techniques.

All measurements should be taken and recorded in metric notation, using a ruler or callipers. All baseline evaluations should be performed as close as possible to the beginning of treatment and never more than four weeks before the beginning of the treatment.

2.0 Methods of Measurement

The same method of assessment and the same technique should be used to characterize each identified and reported lesion at baseline and during follow-up.

CT and MRI scans: CT and MRI are the best currently available and reproducible methods to measure target lesions selected for response assessment. Conventional CT and MRI should be performed with contiguous cuts of 10 mm or less in slice thickness. Spiral CT should be performed using a 5 mm contiguous reconstruction algorithm; this specification applies to tumours of the chest, abdomen and pelvis, while head and neck tumours and those of extremities usually require specific protocols.

Chest X-ray. Lesions on chest X-ray are acceptable as measurable lesions when they are clearly defined and surrounded by aerated lung. However, CT is preferable.

Cytology and histology can be used to differentiate between Partial Response and Complete Response in rare cases (e.g., after treatment to differentiate between residual benign lesions and residual malignant lesions in tumour types such as germ cell tumours).

Clinical examination: Clinically selected lesions will only be considered measurable when they are superficial (e.g., skin nodules and palpable lymph nodes). For the case of skin lesions, documentation by colour photography- including a ruler to estimate the size of the lesion -is recommended.

3.0 Selection of “Target” and “Non-Target” lesions

Target Lesions

All measurable lesions up to a maximum of five lesions per organ and 10 lesions in total, representative of all involved organs, should be identified as *target lesions* and recorded and measured at baseline. Target lesions should be selected on the basis of their size (those with the longest diameter) and their suitability for accurate repeated measurements, either by imaging techniques or clinically. A sum of the longest diameter (LD) for all target lesions will be calculated and reported as the baseline sum LD. The baseline sum LD will be used as reference by which to characterise the objective tumour-response.

Non-Target Lesions

All other lesions (or sites of disease) should be identified as non-target lesions and should also be recorded at baseline. Measurements of these lesions are not required, but the presence or absence of each should be noted throughout follow-up.

4.0 Response

Response criteria for this study are defined below

Evaluation of Target Lesions

Progressive Disease (PD): at least a 20% increase in the sum of the LD of target lesions, taking as reference the smallest sum LD recorded since the treatment started or the appearance of one or more new lesions

Evaluation of Non-Target Lesions

Progressive Disease (PD): Appearance of one or more new lesions and/or unequivocal progression of existing non-target lesions

5.0 Overall Responses

The table below provides overall responses for all possible combinations of tumour responses in target and non-target lesions, with or without the appearance of new lesions.

In assessing tumour progression in this study, only the last three shaded rows in the table on the next page are relevant.

Table of Overall response (taken from RECIST)

Target lesions	Non-Target lesions	New lesions	Overall response
CR	CR	No	CR
CR	Incomplete response/SD	No	PR
PR	Non-PD	No	PR
SD	Non-PD	No	SD
PD	Any	Yes or No	PD
Any	PD	Yes or No	PD
Any	Any	Yes	PD

Patients with a global deterioration of health status requiring discontinuation of treatment without objective evidence of disease progression at that time should be classified as having “symptomatic deterioration”. Every effort should be made to document the objective progression even after discontinuation of treatment.

PROTOCOL APPENDIX 3: EUROQOL EQ-5D & FACT-P QUALITY OF LIFE QUESTIONNAIRES

Health Questionnaire **EQ-5D**

The next few questions are about your general health at present.

For each of the five sets of statements below, please tick the **one** box that best describes your own health state today.

1. Mobility

I have no problems in walking about..... ☐
I have some problems in walking about ..... ☐
I am confined to bed ..... ☐

2. Self-care

I have no problems with self-care..... ☐
I have some problems washing and dressing myself..... ☐
I am unable to wash or dress myself..... ☐

3. Usual activities

(e.g. work, study, housework, family or leisure activities)

I have no problems with performing my usual activities..... ☐
I have some problems with performing my usual activities..... ☐
I am unable to perform my usual activities..... ☐

4. Pain/discomfort

I have no pain or discomfort..... ☐
I have moderate pain or discomfort..... ☐
I have extreme pain or discomfort..... ☐

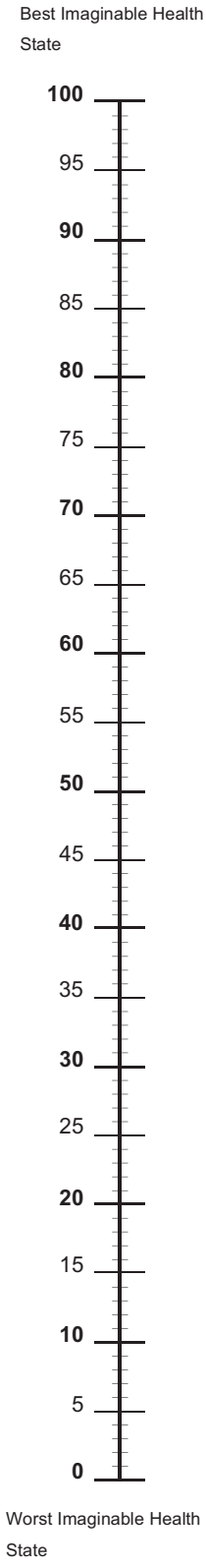
5. Anxiety/depression

I am not anxious or depressed..... ☐
I am moderately anxious or depressed..... ☐
I am extremely anxious or depressed..... ☐

6. Health State Scale

To help people say how good or bad their health is, we have drawn a scale (rather like a thermometer) on which the best health state you can imagine is marked 100 and the worst health state you can imagine is marked 0.

Your own health state today



FACT-P QoL

QUALITY OF LIFE QUESTIONNAIRE
Fact P (Version 4)
Below is a list of statements that other people with your illness have said are important. By circling one (1) number per line, please indicate how true each statement has been for you during the past 7 days.

	PHYSICAL WELL-BEING	Not at all	A little bit	Some-what	Quite a bit	Very much
GP1	I have a lack of energy	0	1	2	3	4
GP2	I have nausea (I feel sick)	0	1	2	3	4
GP3	Because of my physical condition, I have trouble meeting the needs of my family	0	1	2	3	4
GP4	I have pain	0	1	2	3	4
GP5	I am bothered by side effects of treatment	0	1	2	3	4
GP6	I feel ill	0	1	2	3	4
GP7	I am forced to spend time in bed	0	1	2	3	4
	SOCIAL/FAMILY WELL-BEING	Not at all	A little bit	Some-what	Quite a bit	Very much
GS1	I feel close to my friends	0	1	2	3	4
GS2	I get emotional support from my family	0	1	2	3	4
GS3	I get support from my friends	0	1	2	3	4
GS4	My family has accepted my illness	0	1	2	3	4
GS5	I am satisfied with family communication about my illness	0	1	2	3	4
GS6	I feel close to my partner (or the person who is my main support)	0	1	2	3	4
Q1	*Regardless of your current level of sexual activity, please answer the following question. If you prefer not to answer it, please check this box* ☐ *and go to the next section.*					
GS7	I am satisfied with my sex life	0	1	2	3	4

By circling one (1) number per line, please indicate how true each statement has been for you during the past 7 days.

	EMOTIONAL WELL-BEING	Not at all	A little bit	Some-what	Quite a bit	Very much
GE1	I feel sad	0	1	2	3	4
GE2	I am satisfied with how I am coping with my illness	0	1	2	3	4
GE3	I am losing hope in the fight against my illness	0	1	2	3	4
GE4	I feel nervous	0	1	2	3	4
GE5	I worry about dying	0	1	2	3	4
GE6	I worry that my condition will get worse	0	1	2	3	4

	FUNCTIONAL WELL-BEING	Not at all	A little bit	Some-what	Quite a bit	Very much
GF1	I am able to work (include work at home)	0	1	2	3	4
GF2	My work (include work at home) is fulfilling	0	1	2	3	4
GF3	I am able to enjoy life	0	1	2	3	4
GF4	I have accepted my illness	0	1	2	3	4
GF5	I am sleeping well	0	1	2	3	4
GF6	I am enjoying the things I usually do for fun	0	1	2	3	4
GF7	I am content with the quality of my life right now	0	1	2	3	4

By circling one (1) number per line, please indicate how true each statement has been for you during the past 7 days.

	ADDITIONAL CONCERNS	Not at all	A little bit	Some-what	Quite a bit	Very much
C2	I am losing weight	0	1	2	3	4
C6	I have a good appetite	0	1	2	3	4
P1	I have aches and pains that bother me	0	1	2	3	4
P2	I have certain areas of my body where I experience significant pain	0	1	2	3	4
P3	My pain keeps me from doing things I want to do	0	1	2	3	4
P4	I am satisfied with my current level of physical comfort	0	1	2	3	4
P5	I am able to feel like a man	0	1	2	3	4
P6	I have trouble moving my bowels	0	1	2	3	4
P7	I have difficulty urinating (passing water)	0	1	2	3	4
BL2	I urinate more frequently than usual	0	1	2	3	4
P8	My problems with urinating limit my activities	0	1	2	3	4
BL5	I am able to have and maintain an erection	0	1	2	3	4

PROTOCOL APPENDIX 4 – HEALTH ECONOMICS QUESTIONNAIRE

Trapeze health problems questionnaire for patients on study treatment

During the last 3 weeks (i.e. since your last visit to hospital for study treatment) we would like you to tell us about any health problems you may have had. Please answer all of the questions yourself by ticking the box that **best** applies to you.

THE INFORMATION YOU PROVIDE WILL BE KEPT STRICTLY CONFIDENTIAL AND USED ONLY FOR MEDICAL RESEARCH.

1. Talking to a doctor
a) During the three weeks ending yesterday, apart from any visit to a hospital, did you talk to a doctor, either in person or by telephone?

Yes ☐ No ☐ (if no, go straight to question 2)

If Yes:

b) How many times did you talk to a doctor in these two weeks? (please circle)

1 2 3 4 5 6 7 8 9 or more

c) Was this consultation

under the National Health Service, ☐ or paid for privately? ☐

d) Was the doctor

1 a GP (i.e. a family doctor), ☐
2 a specialist, ☐
3 some other kind of doctor? ☐

e) Did you talk to the doctor

1 by telephone, ☐
2 at your home, ☐
3 in the doctor's surgery, ☐
4 at a health centre, ☐
5 elsewhere ☐

f) Did the doctor prescribe you any medication (in addition to your study drugs)?

Yes ☐ No ☐ (If no, please go to question 2)

If yes, was this prescribed over a short period or permanently?

Short ☐ Permanently ☐

Please list prescription medication below:

_____

2. Hospital visits

During the last 3 weeks have you been to hospital for any reason?

Yes ☐ No ☐ (if no, please go to question 3)

If yes, please give details of your attendance or admittance?

1. Out-patient; ☐ how many times _____
2. In patient; ☐ how many days _____
3. Casualty; ☐ how many days _____

3. During the last 3 weeks has a nurse visited you at your home for any reason?

Yes ☐ No ☐ (if no, please go to question 4)

If yes, how many times? _____

4. During the last 3 weeks has anyone from social services or a voluntary organisation visited you at your home for any reason?

Yes ☐ No ☐ (if no, please go to question 5)

If yes, how many times? _____

5. During the last 3 weeks has a relative or friend taken time off work to look after you?

Yes ☐ No ☐

If yes, how many days? _____

<u>If yes to any of the above questions 1 - 6, what was the problem?</u>

_____

_____

_____

TRAPEZE health problems questionnaire for patients on follow-up

During the last 3 months (i.e. since your last visit to hospital) we would like you to tell us about any health problems you may have had. Please answer all the questions yourself by ticking the box that best applies to you.

THE INFORMATION YOU PROVIDE WILL BE KEPT STRICTLY CONFIDENTIAL AND USED ONLY FOR MEDICAL RESEARCH.

1. Talking to a doctor

a) During the three months ending yesterday, apart from any visit to a hospital, did you talk to a doctor, either in person or by telephone?

Yes ☐ No ☐ (if no, go straight to question 2)

If Yes:

b) How many times did you talk to a doctor in these three months? (please circle)

1 2 3 4 5 6 7 8 9 or more

c) Was this consultation

under the National Health Service, ☐ or paid for privately? ☐

d) Was the doctor

1 a GP (i.e. a family doctor), ☐
2 a specialist, ☐
3 some other kind of doctor? ☐

e) Did you talk to the doctor

1 by telephone, ☐
2 at your home, ☐
3 in the doctor's surgery, ☐
4 at a health centre, ☐
5 or elsewhere? ☐

f) Did the doctor prescribe you any medication?

Yes ☐ No ☐

If yes, was this prescribed for use over a short period or permanently?

Short ☐ Permanently ☐

Please list the prescribed medication below:

2. Hospital visits

During the last 3 months have you been to hospital for any reason?

Yes ☐ No ☐ (if no, please go to question 3)

If yes, please give details of your attendance or admittance?

1. Out-patient; ☐ how many times _____
2. In patient; ☐ how many days _____
3. Casualty; ☐ how many days _____

3. During the last 3 months has a nurse visited you at your home for any reason?

Yes ☐ No ☐ (if no, please go to question 4)

If yes, how many times? _____

4. During the last 3 months has anyone from social services or a voluntary organisation visited you at your home for any reason?

Yes ☐ No ☐ (if no, please go to question 5)

If yes, how many times? _____

5. During the last 3 months has a relative or friend taken time off work to look after you?

Yes ☐ No ☐

If yes, how many days? _____

If yes to any of the above questions 1 - 6, what was the problem?

APPENDIX 5: PAIN DIARY SHEETS

TRAPEZE

CONFIDENTIAL

Patient Pain Diary

Patient Initials: ___ ___ ___

(First - middle - last)

Patient Number: _____

Centre Name: _____

Investigator: _____

This diary should be carried with you at all times.

For the seven-day period prior to your next appointment, please complete one page for each day as carefully as possible.

Next appointment: Date: _____

Time: _____

Please take this diary with you when you return to the clinic/hospital:

This patient is in a clinical study. In the event of a medical emergency, please telephone one of the following numbers listed below:

1. _____

2. _____

Patient: please complete the following:

These questions were answered on: 20

Day of week _____ Day _____ Month _____ Year _____

Please list the type of pain relief (analgesic) medication that you have taken over the last 24 hours and the amount. Only information about pain medication is needed. Please do not include medication for other conditions ,(e.g. heart problems)

To be completed by the patient			These shaded boxes to be completed by the clinical Research Nurse/ Associate (*refer to analgesic score table in protocol)			
Product name (trade name and dose)	Type of dose (tablet, injection, patch…)	Number of doses in 24 hours	Type of analgesic and total dose (in 24 hours)	Total dose / analgesic dose (A)	Score value (B)	Total units per 24 hours (A x B)
				Total daily score (C)		

Do you think you have remembered everything you have taken? Yes ☐ No ☐

Present Pain Intensity (PPI)

Please circle the appropriate number according to how much pain you felt on average during the past 24 hours.

0	1	2	3	4	5
No pain	Mild	Discomforting	Distressing	Horrible	Excruciating

Appendix 2 Composition of the Data Monitoring Committee and Trial Steering Committee

Data Monitoring Committee

Professor Mario Eisenberger (Chairperson), Professor of Oncology & Urology, The Blausteine Cancer Research Building, John Hopkins University, Baltimore, MD, USA.

Professor Fred Saad, Professor of Surgery/Urology, Université de Montréal, Chum/Hôpital Notre-Dame, Montreal, Québec, Canada.

Mr Matthew Sydes, Senior Medical Statistician, Medical Research Council, MRC Clinical Trials Unit Aviation House London, UK.

Trial Steering Committee

Professor Richard Gray, Professor of Medical Statistics, Clinical Trial Service Unit and Epidemiological Studies Unit, Oxford, UK.

Professor Noel Clark, Consultant Oncologist, Christie Hospital NHS Foundation Trust, Manchester UK.

Professor Robert Coleman, Cancer Research Building, School of Medicine & Biomedical Sciences, Weston Park Hospital, Sheffield, UK.

Mr John Anderson (deceased 2013), Department of Urology, Royal Hallamshire Hospital, Sheffield, UK.

Appendix 3 Dates of regulatory and ethical approvals and timelines

TABLE 76 Summary of regulatory and ethical approvals and trial milestones

Event	Date
MHRA approval of Phase II stage of trial	11 November 2004
MREC approval of Phase II stage of trial	9 November 2004
– Protocol V4 & patient and GP Information & consent documents V2	
First site opened	1 January 2005
Recruitment of first patient	4 February 2005
Protocol V5 amendment	April 2005
Protocol V6 amendment	June 2005
Protocol V7 amendment	June 2007
MHRA approval of Phase III stage of trial	9 January 2009
MREC approval of Phase III stage of trial	29 January 2009
– Protocol V8 & patient and GP information & consent documents V3	
MHRA approval of CTA amendment	20 January 2011
MREC approval of CTA amendment	17 February 2011
(i.e. generic docetaxel and ZA use)	
Protocol V9 amendment & patient and GP information & consent documents V3	May 2011
Protocol V10 amendment	10 June 2011
Patient information addendum to V3 (for patients randomised to ZA treatment arms)	July 2011
Closure to recruitment	29 February 2012
Protocol V11 amendment	17 February 2012

CTA, Clinical Trials Authorisation.

Appendix 4 Patient information

TRAPEZE

Research Trial Of Treatments For Patients With Bony Metastatic Cancer Of The Prostate

Patient Information Form

Your Oncologist has explained to you that your prostate cancer is no longer responding to hormonal treatment. We would like to invite you to take part in a research trial to treat you with chemotherapy. Before you decide whether to take part it is important for you to understand why the research is being done and what it will involve. Please take time to read the following information carefully and discuss it with friends, relatives and your GP if you wish. Ask us if there is anything that is not clear or if you would like more information. Take time to decide whether or not you wish to take part.

Further information and a summary of the principles of clinical trials can be found on the Cancer Research UK's patient website (www.cancerhelp.org.uk) together with information about this trial.

Purpose of the trial

It is believed that chemotherapy may be beneficial in treating your prostate cancer. Chemotherapy is currently a standard treatment for prostate cancer that has spread to the bone. The main aim of this trial is test the effects of combining two further known treatments for prostate cancer at different time points, with chemotherapy. The three treatments involved in this trial are described below:

- Docetaxel is a chemotherapy drug and is approved in the UK for the treatment of advanced breast and lung cancer. Docetaxel has been approved for use within clinical trials for the treatment of prostate cancer. Recently published studies (including an international prostate cancer clinical trial called TAX-327) demonstrate that docetaxel improves symptom control and survival times.
- Zoledronic acid is a bone-strengthening agent approved in the UK for treating cancer affecting the bone.
- Strontium-89 is a type of radiotherapy (given by an injection), which is also approved in the UK for treating cancer affecting the bone. Early studies show that it may provide additional pain relief when combined with chemotherapy and may improve your condition.

The aim of the trial is to assess how effective and safe zoledronic acid or strontium-89 is in treating your disease when given in combination with chemotherapy.

We aim to recruit 618 evaluable patients with cancer no longer responding to hormone treatment to take part in this trial. The trial will be open to recruitment for up to 5 years. A patient enrolled onto this trial will be expected to visit the hospital every 3 weeks for chemotherapy treatment for 32 weeks. After this period patients will be expected to attend the hospital on a regular basis for a maximum follow-up period of 2 years. This trial may also be known under the shorter title of 'TRAPEZE', named after the treatments involved which include docetaxel, radioisotope and zoledronic acid.

Taking part in the trial

It is up to you to decide whether or not to take part. If you do decide to take part you will be given this information sheet to keep and be asked to sign a consent form. The original consent form will be stored by your hospital and a copy of the consent form will be sent to the coordinating centre.

If you decide to take part you are still free to withdraw at any time and without giving a reason. This will not affect the standard of care you receive.

Description of the trial

When we do not know which way of treating patients is best, we need to make comparisons. Everyone who agrees to take part in this trial will be put into a treatment group.

The treatment you receive will be chosen by a process called randomisation; the treatment is randomly allocated by computer, which is like making a choice by tossing a coin. This means that you have an equal chance of being treated with one of the above treatments. You and your Oncologist will know which treatment you are receiving.

The four treatment groups in this trial are:

(a) Docetaxel
(b) Docetaxel + zoledronic acid
(c) Docetaxel + strontium-89
(d) Docetaxel + zoledronic acid + strontium-89.

If you agree to take part, your Oncologist will perform a number of tests and examinations before, during and after the trial. You will also be asked to complete a number of questionnaires. These are summarised below:

- General medical and physical examinations
- Blood tests
- X-rays, CT and bone scans – to measure your cancer response to treatment
- DXA Scan (bone density scans) – to measure bone density
- Pain diary
- Quality-of-life questionnaires

Docetaxel, zoledronic acid and strontium-89 are given by a drip into a vein in your arm. This is called an infusion. You will receive one of the following treatments:

(a) Docetaxel 75 mg/m^2 as a one hour intravenous infusion every 3 weeks for a maximum of 10 cycles.
(b) Docetaxel as a one hour intravenous infusion every 3 weeks for a maximum of 10 cycles with zoledronic acid every 3 weeks. Zoledronic acid will then continue alone every 4 weeks until you or your Oncologist wishes to discontinue it.
(c) Docetaxel as a one hour intravenous infusion every 3 weeks for a maximum of 10 cycles and one treatment of strontium-89 given 28 days after the sixth dose of docetaxel as a short intravenous injection. Cycles 7–10 will then follow after a 28 day recovery period.
(d) Docetaxel as a 1-hour intravenous infusion every 3 weeks for a maximum of 10 cycles, followed by one treatment of strontium-89 given 28 days after the sixth dose of docetaxel as a short intravenous injection. Cycles 7–10 will then follow after a 28 day recovery period. Zoledronic acid will be given every 3 weeks throughout the treatment, and will then continue alone every 4 weeks until you or your Oncologist wishes to discontinue it.

You may receive less than 10 cycles of docetaxel chemotherapy cycles. The exact number of cycles that you will receive will be determined by your Oncologist after consultation with you.

As part of your main treatment you will also be given steroid tablets (prednisolone) to take during your course of treatment with docetaxel. In addition, you will receive extra steroid tablets (dexamethasone) for a few days around each infusion of chemotherapy to decrease the potential side-effects of docetaxel (allergic reactions and fluid retention).

You will be required to visit the hospital every 3 weeks until the end of therapy. The duration of treatment will be approximately 35 weeks.

After the end of treatment your Oncologist will see you monthly for 3 months and then every 3 months in order to assess the status of your disease.

The flow chart below explains the visits you will make to the hospital and at which time.

Restrictions

It is important that you inform your Oncologist of any changes in your health, whether or not you think it is due to the treatment. You should also tell your Oncologist of any changes to your medicines, either those prescribed by your GP or those you buy at the chemist.

Other treatments available

Your Oncologist will discuss the different treatment options available to treat your disease.

TABLE 77 Tests and procedures that will be carried out during the trial

Tests and procedures	Before start of chemotherapy	Before each administration of chemotherapy	After chemotherapy	Follow-up (every month for 3 months then every 3 months thereafter)
Read information	✓	–	–	–
Sign consent				
Scanning procedures (CT scan, MRI scan, bone scan and\or ultrasound)	✓	–	–	✓ (as clinically indicated)
DXA bone density scan	✓			✓ (1 year after start of treatment)
Other current medication/ side-effect information collected	✓	✓	✓	✓ (30 days after last infusion)
Medical history information collected	✓	–	–	–
Height measured	✓	–	–	–
Weight and physical exam and vital signs	✓	✓	✓	✓
Blood tests including PSA	✓	✓	✓	✓
Pain and quality-of-life assessments	✓	✓	✓	✓

DXA, dual-energy X-ray absorption scan; MRI, magnetic resonance imaging.

Potential side effects and risks

As with all medicines of this type there may be some unwanted side-effects. You should discuss these with your Oncologist. The more common side-effects are listed below; there may also be other side-effects that we cannot predict. Other medicines will be given to make side-effects less serious and less uncomfortable.

With docetaxel you may experience nausea and/or vomiting, mouth irritation, diarrhoea, fatigue, a pins and needles sensation in your hands or feet, hair loss, changes in your skin and nails, muscular pain, decrease in blood cell counts, infection, and swelling due to fluid retention. Your blood pressure may also fall while the drug is being given, and this will be checked carefully. The infusion of docetaxel may cause temporary local irritation and bruises if it is given into a small vein. All these side-effects have been experienced by some patients during previous studies and most of them are reversible. (The items underlined may not be reversible).

With docetaxel + zoledronic acid you may experience the same effects as stated for docetaxel above with a rise in temperature, and flu-like symptoms, consisting of fever and bone pain due to the zoledronic acid. Zoledronic acid may also affect your kidney function. Blood samples will be taken prior to zoledronic acid infusion at every trial visit to check that your kidney function has not been affected. Uncommonly, zoledronic acid can cause breakdown (osteonecrosis) of the jaw. This is associated with long-term use of zoledronic acid (usually over 24 months) particularly in patients who have dental disease. Zoledronic acid should be discontinued if you need a tooth extraction.

With docetaxel + zoledronic acid + strontium-89 you may experience the same side-effects as stated above for docetaxel and zoledronic acid. The addition of strontium-89 to docetaxel and zoledronic acid may cause some bone pain lasting 36 to 72 hours following injection. This can usually be controlled by analgesics (pain killers). Strontium-89 can also affect your blood counts following injection; these will be monitored very closely with regular blood tests.

With docetaxel + strontium-89 the addition of strontium-89 to docetaxel may cause some bone pain lasting 36 to 72 hours following injection. This can usually be controlled by analgesics (pain killers). Strontium-89 can also affect your blood counts following injection; these will be monitored very closely with regular blood tests.

As with any chemotherapy it is possible that your treatment could cause problems to an unborn child. You must take full contraceptive precautions if there is any chance of you fathering a child during and for at least 2 months after the treatment. If you have a fever or bruising after receiving either of the drug combinations, it is important that you contact your Oncologist immediately. If you have a fever your Oncologist will perform some blood tests and may prescribe antibiotics.

For more information about risks and side-effects, ask your Oncologist.

You may require one extra bone scan more than you would if you were not taking part in the trial. You may require one additional CT scan and will receive two additional bone density scans (DXA scans) more than you would receive if you were not taking part in the trial. Any potential health risk associated with these or any of the above scans is considered to be low for a patient with your medical condition.

The radioactive strontium is intended to give a very high radiation dose to any parts of your bones that are involved in your cancer. The rest of your body gets a lower radiation dose and your Oncologist will explain possible side-effects with you. Any potential health risk associated with the radiation is considered to be minimal for a patient with your medical condition.

If you have private medical insurance you may wish to consult your medical insurers before agreeing to take part in the trial. This is to ensure that you participation will not affect your medical insurance cover.

What happens when the research trial stops?

At the end of the research trial, or should you withdraw, your Oncologist will assess your symptoms, discuss your options and prescribe appropriate treatment. Rarely companies sponsoring research studies may decide to stop the trial before it has finished. If this happens, your Oncologist will explain the reasons why and arrange appropriate care for you.

Potential benefits

The use of chemotherapy may result in a decrease in pain, improvement in the quality of life and a delay in the progression of your disease and improved survival times. This may be further improved by combining chemotherapy with zoledronic acid and/or strontium-89.

The information we get from this trial may help us to treat other patients with cancer more effectively in future.

Looking at blood serum samples

In addition to your routine blood tests we would also like to take additional blood samples from you during your regular trial visits for additional analyses. We would like to monitor changes in protein levels in your blood during treatment to see if it can help us better predict treatment outcomes.

Your participation in this part of the trial is optional and will not affect the treatment that you receive if you do not consent to providing additional blood samples for these additional tests and research.

Looking at tissue samples

As part of the clinical trial we would like to be allowed to have access to samples of your disease tissue, which were taken as part of your routine care and disease diagnoses. These samples will have been collected by your hospital and stored in paraffin fixed wax blocks. If you agree these samples will be collected and tested for the presence of a number of different chemicals known as biological markers by the School of Cancer Sciences at The University of Birmingham and other collaborative centres.

Your participation in this part of the trial is optional and will not affect the treatment that you receive if you do not consent to the research team having access to your stored tissue samples for additional research.

Your rights regarding tissue/blood samples taken as part of this clinical trial

The results of the analysis of your individual samples will not routinely be given to you unless it is of clinical significance and of importance to your health. You will not benefit financially if this research leads to the development of a new treatment or medical test. Any publications resulting from the collection of these tissue or blood samples will be made available to you, if requested.

Please note that your participation in this part of the trial is optional and will not affect the treatment that you receive, if you do not consent to providing additional blood samples or for the research team to have access to your stored tissue samples detailed above.

New information

Sometimes during a trial new information becomes available about the treatment that is being studied. If this happens your Oncologist will tell you about it and discuss with you whether or not you want to continue. If you decide to withdraw your Oncologist will ensure the continuation of your care off trial. You may be asked, if you decide to continue in the trial, to sign a new consent from.

Voluntary participation and discontinuation

Your participation in this trial is voluntary. If you agree to take part and then change your mind and wish to withdraw, you may do so at any time without this decision affecting your future care. If you decide not to take part your Oncologist will discuss your future care with you. Your legal rights will not be affected by your giving consent to participate.

At the end of the trial your Oncologist will discuss future treatment options. It is not anticipated that patients will be switched routinely to the alternative treatment in the trial.

Confidentiality and patient rights

If you agree to take part in the trial you will need to sign and date the Informed Consent Form attached. Your medical notes will need to be seen by authorised members of our research team so they can collect information needed for this research trial and also to check that it is correct. Your unique registration number will be used to make sure you cannot be identified outside the trial. All information collected about you during the course of the research will be treated as strictly confidential. The confidentiality of your medical records will be respected at all times.

We will continue to contact your hospital in the future to find out how you are getting on. Ideally, we would like to do this for life, but patients often change address or can lose touch with their hospital. If this happens we would still like to be able to collect important basic details (e.g. full name, date of birth, hospital number and NHS number). The Office for National Statistics (ONS) keeps records that can easily provide the information we need, so we would like your permission to ask ONS to pass on this information to us. Any information received in this way remains confidential and is used only for the purposes of that particular trial. Please initial the consent form to indicate you are happy for us to do this. The information that will be collected from ONS will relate only to the status of your disease and current health. The ONS system will not be used to collect information such as your home address.

With your consent your GP will be informed that you wish to take part in a clinical trial. Your GP may be asked to provide information from your records, which are required for the trial.

Anonymised data from the trial may be provided to third parties (e.g. pharmaceutical companies or other academic institutions) for research, safety monitoring or licensing purposes.

Your legal rights will not be affected by agreeing to take part in or withdrawing from the trial. You are free to withdraw from the trial at any time without giving a reason. If you decide to withdraw from the trial, this will not affect the standard of your routine care in any way. Your Oncologist will continue to treat you with the same level of care.

The trial has been reviewed and approved by the South West Multicentre Research Ethics Committee, one of 13 national Research Ethics Committees.

You will be informed of any significant new findings that occur during the trial as this may change your decision to continue.

What if something goes wrong?

You will be closely monitored both during and after therapy and any side effects will be treated as appropriate.

If you are harmed by taking part in this research project, there are no special compensation arrangements. If you are harmed due to someone's negligence, then you may have grounds for legal action but you may have to pay for legal advice. Regardless of this, if you wish to complain about any aspect of the way you have been approached or treated during the course of this trial, the normal National Health Service complaints mechanisms are available to you.

Results of the trial

At the end of the trial the information collected will be analysed and published in recognised medical journals. Your Oncologist will be informed of any publications and will be able to supply a copy of these publications to you on request. The identity of the patients who took part in the trial will remain confidential. Your Oncologist and trial nurse will also be informed of any results throughout the duration of the trial.

Organisation and funding of the trial

The research trial is being carried out by the Cancer Research UK, School of Cancer Sciences at The University of Birmingham. The research is funded by grants from the Health Technology Assessment (HTA) programme (a governmental funding body which funds clinical research), and pharmaceutical companies Sanofi-aventis and Novartis Pharmaceuticals UK Ltd. During your involvement in this trial no travel costs incurred by you or you family will be paid. Your Oncologist or any other members of staff that are involved in your treatment and care have not been paid for entering you into this clinical trial or receive payment for conducting the trial.

Time to consider

You should take at least 24 hours to decide if you wish to take part.

Who should you contact with questions?

You will be given a copy of this information sheet and the signed consent form to keep. If you have any problems or questions about this trial or your rights as a patient in clinical research you should contact:

Oncologist . . . . . Tel No . . . . . .

Trial Nurse . . . . . Tel No . . . . . .

24 hour contact number: . . . . . .

The 24 hour contact number can be used out of working hours (9am – 5pm) in the event where you need you contact a hospital doctor immediately.

We would like to thank you for reading the Patient Information Sheet and for considering taking part in this Clinical Trial. If you have any further questions please talk to the trial doctor before considering entry into this clinical trial.

TRAPEZE

Research Trial of Treatments for Patients with Bony Metastatic Cancer of the Prostate

Patient Consent Form

	Please initial
I have been given a copy of the Patient Information Sheet (version 4, 12-Apr-2011) for this study. I have read and understood it and I have had the opportunity to ask questions and discuss the study.	☐
If I want to ask any further questions I understand that I may contact the Study Doctor or his/her colleagues or staff.	☐
I understand that I must tell the Study Doctor (or his/her nominee) if I notice any unusual or unexpected effects or if my health changes.	☐
I give permission for my GP to be informed of my participation and sent details of the study.	☐
I give permission for my name and a copy of this consent form, to be given to the study office when I am registered into the study.	☐
I understand that my medical records may need to be reviewed by responsible individuals from the trials office, or from regulatory authorities where it is relevant to my taking part in research. I give permission for these individuals to have access to my records. However, I understand that I will not be identified by name in any reports or publications resulting from this study.	☐
I also understand that data collected about me for this study will be held under the provisions of the 1998 Data Protection Act and will be stored in manual and electronic files in a secure encoded format	☐
I understand that I may withdraw from the Study at any time, without giving a reason and without affecting any medical treatment I will receive.	☐
I give permission for ONS (Office of National Statistics) to pass information on from my records for the TRAPEZE trial.	☐
I voluntarily agree to participate in the TRAPEZE study	☐
I give permission for samples of tissue previously taken (Tissue blocks) and tissue left over from Surgery and routine investigations to be used for related laboratory research that may be conducted in the future. (I*f the answer to this question is 'NO', you may still take part in this study)*	☐ YES ☐ NO ☐
I give permission for extra blood samples to be taken and used for additional related laboratory studies. I understand that I am free to withdraw my approval for use of these samples at any time without giving a reason and without my medical care and legal rights being affected. (I*f the answer to this question is 'NO', you may still take part in this study)*	☐ YES ☐ NO ☐
I have been given a copy of the quality of life Patient Booklet and I agree to take part in the quality of life study. *(If the answer to this question is 'NO', you may still take part in this study)*	☐ YES ☐ NO ☐

Name of Patient	Signature	Date

I certify that I have explained to the above patient the nature and purpose, the potential benefits, and possible risks associated with participation in this research study. I have answered all questions that have been raised.

Name of Investigator	Signature	Date

A randomised phase II/III trial of Docetaxel plus Prednisolone vs. Docetaxel plus Prednisolone plus Zoledronic Acid vs. Docetaxel plus Prednisolone plus Strontium-89 vs. Docetaxel plus Prednisolone vs. Docetaxel plus Prednisolone plus Zoledronic Acid plus Strontium-89 in Hormone-refractory Prostate Cancer Metastatic to bone

The TRAPEZE Trial

GP Information Sheet

Your patient has been entered into the TRAPEZE trial for the treatment of their hormone-refractory prostate cancer, which is now metastatic to bone. This is a Phase II/III randomised controlled trial that aims to recruit 618 evaluable patients over 6 years from approximately up to 50 hospitals throughout the UK. The trial will close to recruitment at the end of February 2012. The trial is being coordinated by the CR UK Clinical Trials Unit (CRCTU) at the University of Birmingham. This sheet provides information on the rationale behind the trial and what it will involve for your patient.

Aim of the trial

The treatment of hormone-refractory disease is problematical. There is evidence that cytotoxic chemotherapy can help control symptoms and improve survival. As the disease commonly affects the bones (in around 80% of men) agents targeting bone disease are frequently used. Zoledronic acid has been shown to delay worsening of bone disease and help control pain. There is also laboratory evidence suggesting it may kill prostate cancer cells when combined with chemotherapy.

We therefore wish to examine whether the addition of zoledronic acid to chemotherapy will improve outcomes, including survival, in patients with hormone-refractory disease affecting bone.

Strontium-89 is a radioactive drug which is actively taken up from the blood by bone deposits of the cancer, resulting in targeted radiotherapy. It has also been shown to slow down bone disease and improve pain control. A previous small trial has suggested that there may be benefits from combining Strontium-89 with chemotherapy and we wish to verify or refute this in a larger trial with modern chemotherapy.

Treatment allocation

The details of the trial have been discussed with your patient by their clinician and trial nurse and written informed consent has been obtained. It has been made clear to the patient that they are free to withdraw from the trial at any time without needing to justify their decision and without affecting their future care.

Patients are randomised via computer randomisation at the CRCTU Birmingham, into one of the four possible treatment arms below:

(a) Docetaxel 75 mg/m^2 as a one hour intravenous infusion every 3 weeks for a maximum of 10 cycles.
(b) Docetaxel as above with Zoledronic acid every 3 weeks.
(c) Docetaxel as above and Strontium-89 given 28 days after the Cycle 6 docetaxel, as a short intravenous injection. Docetaxel may be continued for up to 10 cycles at his clinician's discretion, restarting at least one month after the Strontium-89 injection.
(d) Docetaxel plus Zoledronic acid and Strontium-89, administered as above. Docetaxel may be continued up to 10 cycles, as above.

Patients are allocated a trial number and been informed as to which of the above treatment arms they have been randomised to.

Possible side effects

Your patient is likely to experience some side-effects associated with the allocated treatment. The more common side-effects are listed below, but there may also be others that we cannot predict.

Docetaxel:

- Nausea and/or vomiting
- Myelosuppression – Neutropenia, Thrombocytopenia.
- Allergy (Anaphylactic and Hypersensitivity reactions)
- Diarrhoea
- Stomatitis
- Peripheral neuropathy
- Skin toxicity
- Alopecia
- Liver toxicity
- Fluid retention
- Hyperlacrimation
- Fatigue

Zoledronic acid treatment arms (b + d): The patient may experience the same effects as stated for Docetaxel above plus a rise in temperature, and flu-like symptoms, consisting of fever and bone pain due to the zoledronic acid. Long-term use (i.e. > 24 months) of zoledronic acid use has been linked to osteonecrosis of the jaw. This is particularly of concern in patients who have dental disease. Zoledronic acid should be discontinued if a patient requires dental extraction.

Strontium-89 treatment arms (c + d): The addition of strontium-89 to docetaxel may cause some bone pain lasting 36 to 72 hours following injection. This will be controlled by analgesics. Strontium-89 may also affect marrow reserve. Blood counts will be monitored very closely and strontium-89 will be omitted if there is inadequate marrow reserve.

Your patient has been given a 24 hour contact number to call in the event of suspected neutropenic sepsis, or any other clinical problems arising while on the trial.

The trial will be monitored by an independent data and safety monitoring committee. The committee will advise on whether the trial should be continued in respect to patient safety and results arising from the trial and any other relevant studies.

Quality of life

As part of the TRAPEZE trial, we are also keen to investigate how treatments might affect patients' quality of life and general well-being. If your patient has agreed to enter this part of the trial they will be asked to complete two questionnaires about their quality of life and general health at each trial visit.

Additional pathology studies

The CRCTU is also interested in biological predictive markers of treatment benefit or toxicity. For this purpose, we have also requested permission from your patient to access a tissue sample from their surgery/biopsy of their prostate, done as part of routine clinical practice. We have also sought consent from your patient for the collection and storage of blood samples taken at intervals during the trial for future proteomic analysis of both known and novel protein markers, using the expertise within the School of Cancer Sciences at the University of Birmingham and other collaborative centres.

Patient confidentiality

All information about your patient will be treated in the strictest of confidence and nothing that may identify them will be revealed to any third parties. Access to your patient's medical records may be required by authorised members of our research team, to enable them to retrieve or validate information needed for the trial. Unless your patient has given permission for their name to be collected, all research data held centrally at CRCTU about them will be anonymised and identified only by a unique trial number, initials and data of birth.

Contacts

If you have any further questions regarding your patient's participation in the TRAPEZE trial please do not hesitate to contact your patient's treating clinician, trial nurse or the TRAPEZE trial office on the numbers below.

Your patient's clinician is:		
Contact number:		
24 hour Hospital switchboard number:		
TRAPEZE Trial Office:	XXXXX	(Mon-Fri 08.00 – 16.00 hrs)

Appendix 5 Results tables and figures

TABLE 78 Patients who have withdrawn full consent

Centre	Date of Randomisation	TNO	Randomised treatment
Queen Elizabeth Hospital	6 January 2006	51	Docetaxel ZA Sr-89
Queen Elizabeth Hospital	27 January 2006	60	Docetaxel Sr-89
Queen Elizabeth Hospital	7 March 2006	70	Docetaxel
Queen Elizabeth Hospital	25 August 2006	115	Docetaxel ZA
Western Infirmary	18 December 2006	140	Docetaxel Sr-89
Western General Hospital	16 August 2007	194	Docetaxel Sr-89
Western General Hospital	6 February 2008	241	Docetaxel Sr-89
Queen Elizabeth Hospital	29 September 2008	289	Docetaxel ZA
Western General Hospital	5 August 2009	389	Docetaxel ZA
Royal Free Hospital	9 November 2009	422	Docetaxel ZA
Queen Elizabeth Hospital	11 June 2010	477	Docetaxel ZA
Queen Elizabeth Hospital	7 July 2010	485	Docetaxel ZA
Huddersfield Royal Infirmary	15 July 2010	488	Docetaxel ZA Sr-89
Western General Hospital	5 October 2010	523	Docetaxel
Weston General Hospital	5 November 2010	545	Docetaxel
Royal Derby Hospital	8 November 2010	546	Docetaxel
Royal Derby Hospital	11 November 2010	551	Docetaxel ZA
Aberdeen Royal Infirmary	19 November 2010	557	Docetaxel ZA Sr-89
Western General Hospital	30 November 2010	561	Docetaxel ZA
Queen Elizabeth Hospital	21 January 2011	579	Docetaxel ZA
Huddersfield Royal Infirmary	5 April 2011	609	Docetaxel
Christie Hospital	5 April 2011	610	Docetaxel ZA
Royal Preston Hospital	11 May 2011	623	Docetaxel Sr-89
Western General Hospital	31 August 2011	679	Docetaxel
St Mary's Hospital	4 January 2012	725	Docetaxel ZA
Huddersfield Royal Infirmary	23 January 2012	740	Docetaxel Sr-89
Bradford Royal Infirmary	2 February 2012	743	Docetaxel ZA
Royal Preston Hospital	13 February 2012	748	Docetaxel ZA

TNO, trial number.

TABLE 79 Recruitment by centre

Randomisation centre	Docetaxel, *n* (*N* = 191)	Docetaxel + ZA, *n* (*N* = 188)	Docetaxel + Sr-89, *n* (*N* = 190)	Docetaxel + ZA + Sr-89, *n* (*N* = 188)	Overall, *n* (*N* = 757)
Aberdeen Royal Infirmary	5	5	5	6	21
Ayr Hospital	5	6	5	5	21
Bradford Royal Infirmary	3	4	4	2	13
Cheltenham General Hospital	4	4	4	4	16
Christie Hospital	30	31	30	31	122
Dorset County Hospital	2	1	1	1	5
Forth Valley Royal Hospital	2	1	2	1	6
Gloucester Royal Hospital	0	0	1	0	1
Huddersfield Royal Infirmary	2	2	3	2	9
Ipswich Hospital	5	4	4	4	17
Maidstone Hospital	7	7	7	8	29
Poole Hospital	0	0	0	1	1
Queen Elizabeth Hospital	32	31	32	31	126
Royal Albert Edward Infirmary	2	1	2	2	7
Royal Bournemouth Hospital	2	1	1	1	5
Royal Derby Hospital	6	6	7	7	26
Royal Free Hospital	3	4	2	3	12
Royal Marsden Hospital London	1	0	0	0	1
Royal Marsden Hospital Sutton	7	8	7	8	30
Royal Preston Hospital	9	9	8	8	34
Southampton General Hospital	4	3	4	3	14
St James's University Hospital	7	7	7	6	27
Queen Alexandra Hospital	4	5	4	4	17
Velindre Hospital	1	2	2	2	7
Western General Hospital	28	27	28	28	111
Beatson West of Scotland Cancer Centre	15	15	15	16	61
Weston General Hospital	3	3	4	3	13
Wishaw General Hospital	2	1	1	1	5

TABLE 80 Ineligible patients

Centre	Date of randomisation	TNO	Randomised treatment	Reason for ineligibility
Queen Elizabeth Hospital	18 May 2005	2	Docetaxel + ZA + Sr-89	No proof of progression on study entry. Patient was referred from an external hospital and not all results were here. Please see principal investigator for further information
Western General Hospital	10 November 2005	41	Docetaxel + Sr-89	Baseline BP not recorded
Christie Hospital	4 January 2006	49	Docetaxel + Sr-89	4 January 2006 – PSA progression not demonstrated
Western General Hospital	1 February 2006	62	Docetaxel	Computed tomography and bone scan done after randomisation
Western General Hospital	10 October 2006	129	Docetaxel + ZA	Baseline bloods not within 28 days of randomisation
Beatson West of Scotland Cancer Centre	23 November 2006	136	Docetaxel	Haemoglobin and AST were not within the levels specified for entry – waiver not requested
Queen Elizabeth Hospital	25 January 2007	147	Docetaxel + Sr-89	Patient GP/urologists stopped Zoladex® (AstraZeneca) prior study entry. We were not informed
Western General Hospital	22 February 2008	245	Docetaxel + ZA	Bicalutamide not stopped before 25 January 2008 and no baseline bloods prior to randomisation
Royal Marsden Hospital Sutton	19 December 2008	313	Docetaxel + ZA + Sr-89	Inadequate haematological function (Hb < 10 g/dl)
Beatson West of Scotland Cancer Centre	26 February 2009	334	Docetaxel + ZA + Sr-89	On-study bloods more than 14 days before cycle 1
Wishaw General Hospital	3 April 2009	343	Docetaxel + ZA	Stop date of bicalutamide not known
Royal Marsden Hospital Sutton	17 April 2009	345	Docetaxel + Sr-89	Bicalutamide not stopped 4 weeks before treatment start as clinician wanted patient to start chemotherapy earlier as high risk of developing cord compression
St James's University Hospital	21 April 2009	346	Docetaxel + Sr-89	On-study bloods not within 28-day time frame
Dorset County Hospital	15 July 2009	381	Docetaxel	Patient did not discontinue bicalutamide until 7 July 2009 – discussed/agreed by Darren Barton, TC
Western General Hospital	5aug2009	389	Docetaxel + ZA	Haematology not within 28 days
Christie Hospital	20 August 2009	394	Docetaxel + ZA	Patients PSA was only 4.4 on randomisation and there is no evidence of new bone mets. His PSA on his first treatment cycle was 6.5
Maidstone Hospital	12 January 2010	438	Docetaxel + ZA	BP not done at baseline
Western General Hospital	7 July 2010	486	Docetaxel + Sr-89	Baseline BP not recorded in error

continued

TABLE 80 Ineligible patients (*continued*)

Centre	Date of randomisation	TNO	Randomised treatment	Reason for ineligibility
Bradford Royal Infirmary	13 October 2010	531	Docetaxel + ZA	Prior estramustine therapy – randomised 5 days short of 4 weeks
St James's University Hospital	9 November 2010	547	Docetaxel + ZA	No chest scans at baseline
Huddersfield Royal Infirmary	17 November 2010	556	Docetaxel + Sr-89	Patient randomised too early in error so bicalutamide date is before 4 weeks; treatment did not commence until after 4 weeks
Huddersfield Royal Infirmary	29 November 2010	559	Docetaxel	BP not done at baseline
Queen Alexandra Hospital	21 December 2010	569	Docetaxel	Not 4 weeks between stopping bicalutamide – was 4 weeks before starting treatment
Dorset County Hospital	16 February 2011	589	Docetaxel + ZA	Baseline bloods taken 17 January 2011, randomised 16 February 2011, outside 28-day time-period
Royal Derby Hospital	4 April 2011	607	Docetaxel + ZA	Bicalutamide stop date not 4 weeks
Royal Marsden Hospital Sutton	23 June 2011	643	Docetaxel + ZA + Sr-89	Patient had dental extractions before first cycle meaning they were unfit to receive ZA until cycle 4
Christie Hospital	15 February 2012	749	Docetaxel + ZA + Sr-89	Still taking a bisphosphonate

AST, aspartate aminotransferase; BP, blood pressure; GP, general practitioner; TC, trial co-ordinator; TNO, trial number.

TABLE 81 Sequence of treatment forms returned by randomisation arms

	Docetaxel (*N* = 191)		Docetaxel + ZA (*N* = 188)		Docetaxel + Sr-89 (*N* = 190)		Docetaxel + ZA + Sr-89 (*N* = 188)		Overall (*N* = 757)	
Sequence	*n*	%	*n*	%	*n*	%	*n*	%	*n*	%
0	5	2.6	8	4.3	9	4.7	6	3.2	28	3.7
1	7	3.7	13	6.9	6	3.2	11	5.9	37	4.9
1–2	9	4.7	4	2.1	9	4.7	5	2.7	27	3.6
1–2–3	12	6.3	7	3.7	14	7.4	9	4.8	42	5.5
1–2–3–4	10	5.2	8	4.3	8	4.2	9	4.8	35	4.6
1–2–3–4–5	20	10.5	14	7.4	14	7.4	9	4.8	57	7.5
1–2–3–4–5–6	83	43.5	77	41	81	42.6	88	46.8	329	43.5
1–2–3–4–5–6–7	7	3.7	4	2.1	5	2.6	7	3.7	23	3
1–2–3–4–5–6–7–8	4	2.1	10	5.3	4	2.1	5	2.7	23	3
1–2–3–4–5–6–7–8–9	8	4.2	8	4.3	5	2.6	4	2.1	25	3.3
1–2–3–4–5–6–7–8–9–10	26	13.6	33	17.6	35	18.4	33	17.6	127	16.8
1–2–3–4–5–7–8	0	0	0	0	0	0	1	0.5	1	0.1
1–2–3–4–5–7–8–10	0	0	0	0	0	0	1	0.5	1	0.1
1–2–3–4–5–7–8–9	0	0	1	0.5	0	0	0	0	1	0.1
1–2–3–4–5–7–8–9–10	0	0	1	0.5	0	0	0	0	1	0.1
Total	191	100.0	188	100.0	190	100.0	188	100.0	757	100.0

TABLE 82 Sequence of treatment by comparisons

	No ZA (*N* = 381)		ZA (*N* = 376)		No Sr-89 (*N* = 379)		Sr-89 (*N* = 378)	
Sequence	*n*	%	*n*	%	*n*	%	*n*	%
0	14	3.7	14	3.7	13	3.4	15	4
1	13	3.4	24	6.4	20	5.3	17	4.5
1–2	18	4.7	9	2.4	13	3.4	14	3.7
1–2–3	26	6.8	16	4.3	19	5	23	6.1
1–2–3–4	18	4.7	17	4.5	18	4.7	17	4.5
1–2–3–4–5	34	8.9	23	6.1	34	9	23	6.1
1–2–3–4–5–6	164	43	165	43.9	160	42.2	169	44.7
1–2–3–4–5–6–7	12	3.1	11	2.9	11	2.9	12	3.2
1–2–3–4–5–6–7–8	8	2.1	15	4	14	3.7	9	2.4
1–2–3–4–5–6–7–8–9	13	3.4	12	3.2	16	4.2	9	2.4
1–2–3–4–5–6–7–8–9–10	61	16	66	17.6	59	15.6	68	18
1–2–3–4–5–7–8	0	0	1	0.3	0	0	1	0.3
1–2–3–4–5–7–8–10	0	0	1	0.3	0	0	1	0.3
1–2–3–4–5–7–8–9	0	0	1	0.3	1	0.3	0	0
1–2–3–4–5–7–8–9–10	0	0	1	0.3	1	0.3	0	0
Total	381	100	376	100	379	100	378	100

TABLE 83 Number of patients taking concomitant medications by randomisation arms

Concomitant medications	Arm	Patients	%	On-study	%	Pre-CPFS	%	Post-CPFS	%
Antacids and simeticone (GI)	Docetaxel	7	0.92	2	0.26	4	0.53	2	0.29
	Docetaxel + ZA	6	0.79	2	0.26	4	0.53	0	0.00
	Docetaxel + Sr-89	8	1.06	1	0.13	6	0.79	0	0.00
	Docetaxel + ZA + Sr-89	8	1.06	1	0.13	5	0.66	2	0.29
Antispasmodics	Docetaxel	6	0.79	2	0.26	3	0.40	1	0.14
	Docetaxel + ZA	2	0.26	1	0.13	1	0.13	0	0.00
	Docetaxel + Sr-89	2	0.26	0	0.00	2	0.26	0	0.00
	Docetaxel + ZA + Sr-89	3	0.40	2	0.26	1	0.13	0	0.00
H2 antagonist and ulcer healing (GI)	Docetaxel	6	0.79	4	0.53	0	0.00	1	0.14
	Docetaxel + ZA	4	0.53	3	0.40	1	0.13	0	0.00
	Docetaxel + Sr-89	2	0.26	2	0.26	1	0.13	0	0.00
	Docetaxel + ZA + Sr-89	10	1.32	8	1.06	1	0.13	1	0.14
Proton pump inhibitors (GI)	Docetaxel	82	10.83	57	7.53	26	3.43	5	0.72
	Docetaxel + ZA	84	11.10	59	7.79	23	3.04	4	0.57
	Docetaxel + Sr-89	75	9.91	46	6.08	26	3.43	8	1.15
	Docetaxel + ZA + Sr-89	74	9.78	53	7.00	24	3.17	4	0.57
Antimotility, antidiarrhoea (GI)	Docetaxel	21	2.77	1	0.13	18	2.38	2	0.29
	Docetaxel + ZA	10	1.32	2	0.26	7	0.92	0	0.00
	Docetaxel + Sr-89	15	1.98	1	0.13	13	1.72	0	0.00
	Docetaxel + ZA + Sr-89	6	0.79	1	0.13	4	0.53	1	0.14
Laxatives (GI)	Docetaxel	39	5.15	25	3.30	13	1.72	5	0.72
	Docetaxel + ZA	58	7.66	42	5.55	17	2.25	3	0.43
	Docetaxel + Sr-89	49	6.47	25	3.30	17	2.25	9	1.29
	Docetaxel + ZA + Sr-89	49	6.47	29	3.83	17	2.25	7	1.01

Concomitant medications	Arm	Patients	%	On-study	%	Pre-CPFS	%	Post-CPFS	%
Cardiac glycoside (cardiac)	Docetaxel	2	0.26	2	0.26	1	0.13	0	0.00
	Docetaxel + ZA	13	1.72	12	1.59	2	0.26	0	0.00
	Docetaxel + Sr-89	2	0.26	2	0.26	0	0.00	0	0.00
	Docetaxel + ZA + Sr-89	6	0.79	5	0.66	0	0.00	0	0.00
Diuretics (cardiac)	Docetaxel	38	5.02	26	3.43	12	1.59	4	0.57
	Docetaxel + ZA	43	5.68	32	4.23	14	1.85	0	0.00
	Docetaxel + Sr-89	35	4.62	26	3.43	8	1.06	5	0.72
	Docetaxel + ZA + Sr-89	36	4.76	28	3.70	10	1.32	0	0.00
Drugs for arrhythmias (cardiac)	Docetaxel	4	0.53	1	0.13	2	0.26	0	0.00
	Docetaxel + ZA	1	0.13	1	0.13	0	0.00	0	0.00
	Docetaxel + Sr-89	4	0.53	1	0.13	3	0.40	0	0.00
	Docetaxel + ZA + Sr-89	1	0.13	0	0.00	1	0.13	0	0.00
Beta-blockers (cardiac)	Docetaxel	19	2.51	16	2.11	1	0.13	1	0.14
	Docetaxel + ZA	28	3.70	26	3.43	1	0.13	0	0.00
	Docetaxel + Sr-89	28	3.70	27	3.57	2	0.26	1	0.14
	Docetaxel + ZA + Sr-89	34	4.49	29	3.83	6	0.79	0	0.00
Calcium-channel blockers (cardiac)	Docetaxel	26	3.43	23	3.04	4	0.53	0	0.00
	Docetaxel + ZA	25	3.30	23	3.04	1	0.13	1	0.14
	Docetaxel + Sr-89	27	3.57	25	3.30	5	0.66	1	0.14
	Docetaxel + ZA + Sr-89	27	3.57	26	3.43	2	0.26	0	0.00

continued

TABLE 83 Number of patients taking concomitant medications by randomisation arms (*continued*)

Concomitant medications	Arm	Patients	%	On-study	%	Pre-CPFS	%	Post-CPFS	%
Cardiac – other	Docetaxel	14	1.85	11	1.45	3	0.40	0	0.00
	Docetaxel + ZA	23	3.04	23	3.04	0	0.00	0	0.00
	Docetaxel + Sr-89	18	2.38	18 2.	38	1	0.13	1	0.14
	Docetaxel + ZA + Sr-89	23	3.04	22	2.91	1	0.13	0	0.00
Anticoagulants antiplatelet drugs	Docetaxel	69	9.11	45	5.94	27	3.57	5	0.72
	Docetaxel + ZA	66	8.72	43	5.68	26	3.43	4	0.57
	Docetaxel + Sr-89	69	9.11	45	5.94	21	2.77	11	1.58
	Docetaxel + ZA + Sr-89	66	8.72	45	5.94	27	3.57	5	0.72
Blood bone marrow disorders	Docetaxel	35	4.62	8	1.06	24	3.17	5	0.72
	Docetaxel + ZA	27	3.57	3	0.40	21	2.77	6	0.86
	Docetaxel + Sr-89	31	4.10	3	0.40	20	2.64	6	0.86
	Docetaxel + ZA + Sr-89	27	3.57	3	0.40	19	2.51	5	0.72
Bronchodilators antihistamines	Docetaxel	25	3.30	11	1.45	13	1.72	3	0.43
	Docetaxel + ZA	28	3.70	10	1.32	15	1.98	2	0.29
	Docetaxel + Sr-89	28	3.70	15	1.98	12	1.59	6	0.86
	Docetaxel + ZA + Sr-89	30	3.96	14	1.85	15	1.98	4	0.57
Hypnotics (CNS)	Docetaxel	11	1.45	6	0.79	3	0.40	2	0.29
	Docetaxel + ZA	6	0.79	2	0.26	4	0.53	0	0.00
	Docetaxel + Sr-89	11	1.45	8	1.06	2	0.26	1	0.14
	Docetaxel + ZA + Sr-89	9	1.19	4	0.53	3	0.40	2	0.29
Anxiolytics (CNS)	Docetaxel	4	0.53	2	0.26	0	0.00	2	0.29
	Docetaxel + ZA	3	0.40	1	0.13	1	0.13	1	0.14
	Docetaxel + Sr-89	4	0.53	1	0.13	3	0.40	0	0.00
	Docetaxel + ZA + Sr-89	4	0.53	1	0.13	3	0.40	0	0.00

Concomitant medications	Arm	Patients	%	On-study	%	Pre-CPFS	%	Post-CPFS	%
Antiemetics	Docetaxel	62	8.19	13	1.72	51	6.74	7	1.01
	Docetaxel + ZA	71	9.38	15	1.98	54	7.13	12	1.72
	Docetaxel + Sr-89	59	7.79	7	0.92	44	5.81	11	1.58
	Docetaxel + ZA + Sr-89	65	8.59	13	1.72	50	6.61	16	2.30
Central nervous – other	Docetaxel	1	0.13	1	0.13	0	0.00	0	0.00
Antibacterials, antifungals and antiviral	Docetaxel	103	13.61	14	1.85	94	12.42	15	2.16
	Docetaxel + ZA	91	12.02	10	1.32	82	10.83	13	1.87
	Docetaxel + Sr-89	98	12.95	15	1.98	84	11.10	13	1.87
	Docetaxel + ZA + Sr-89	80	10.57	10	1.32	68	8.98	9	1.29
Diabetes drugs	Docetaxel	14	1.85	12	1.59	2	0.26	0	0.00
	Docetaxel + ZA	15	1.98	13	1.72	3	0.40	0	0.00
	Docetaxel + Sr-89	15	1.98	8	1.06	7	0.92	1	0.14
	Docetaxel + ZA + Sr-89	16	2.11	14	1.85	1	0.13	1	0.14
Nitrate	Docetaxel	13	1.72	11	1.45	2	0.26	1	0.14
	Docetaxel + ZA	15	1.98	14	1.85	2	0.26	0	0.00
	Docetaxel + Sr-89	17	2.25	13	1.72	3	0.40	1	0.14
	Docetaxel + ZA + Sr-89	11	1.45	9	1.19	2	0.26	0	0.00
ACE inhibitor	Docetaxel	34	4.49	29	3.83	5	0.66	1	0.14
	Docetaxel + ZA	27	3.57	23	3.04	4	0.53	1	0.14
	Docetaxel + Sr-89	25	3.30	23	3.04	2	0.26	0	0.00
	Docetaxel + ZA + Sr-89	36	4.76	34	4.49	6	0.79	1	0.14
Chemotherapy	Docetaxel	33	4.36	0	0.00	17	2.25	17	2.44
	Docetaxel + ZA	31	4.10	0	0.00	17	2.25	17	2.44
	Docetaxel + Sr-89	36	4.76	0	0.00	17	2.25	20	2.87
	Docetaxel + ZA + Sr-89	43	5.68	0	0.00	18	2.38	25	3.59

continued

TABLE 83 Number of patients taking concomitant medications by randomisation arms (*continued*)

Concomitant medications	Arm	Patients	%	On-study	%	Pre-CPFS	%	Post-CPFS	%
Statin	Docetaxel	46	6.08	40	5.28	7	0.92	0	0.00
	Docetaxel + ZA	47	6.21	44	5.81	3	0.40	1	0.14
	Docetaxel + Sr-89	51	6.74	49	6.47	6	0.79	1	0.14
	Docetaxel + ZA + Sr-89	47	6.21	45	5.94	3	0.40	1	0.14
Antidepressant	Docetaxel	22	2.91	18	2.38	5	0.66	1	0.14
	Docetaxel + ZA	13	1.72	8	1.06	4	0.53	1	0.14
	Docetaxel + Sr-89	20	2.64	17	2.25	4	0.53	1	0.14
	Docetaxel + ZA + Sr-89	16	2.11	11	1.45	1	0.13	4	0.57
Alpha blocker	Docetaxel	24	3.17	19	2.51	6	0.79	2	0.29
	Docetaxel + ZA	19	2.51	15	1.98	4	0.53	1	0.14
	Docetaxel + Sr-89	30	3.96	26	3.43	9	1.19	0	0.00
	Docetaxel + ZA + Sr-89	27	3.57	22	2.91	11	1.45	0	0.00
COX-2 selective inhibitor	Docetaxel	1	0.13	0	0.00	1	0.13	0	0.00
Steroid	Docetaxel	89	11.76	19	2.51	59	7.79	31	4.45
	Docetaxel + ZA	88	11.62	18	2.38	59	7.79	21	3.02
	Docetaxel + Sr-89	75	9.91	14	1.85	45	5.94	29	4.17
	Docetaxel + ZA + Sr-89	77	10.17	23	3.04	53	7.00	27	3.88
Supplement	Docetaxel	23	3.04	15	1.98	6	0.79	1	0.14
	Docetaxel + ZA	51	6.74	13	1.72	36	4.76	4	0.57
	Docetaxel + Sr-89	21	2.77	10	1.32	10	1.32	5	0.72
Enzyme inhibitor	Docetaxel + ZA	1	0.13	0	0.00	0	0.00	1	0.14
Immunosuppressive	Docetaxel + ZA	1	0.13	1	0.13	1	0.13	0	0.00
	Docetaxel + ZA + Sr-89	1	0.13	1	0.13	0	0.00	0	0.00

Concomitant medications	Arm	Patients	%	On-study	%	Pre-CPFS	%	Post-CPFS	%
Radiotherapy	Docetaxel	87	11.49	0	0.00	5	0.66	82	11.78
	Docetaxel + ZA	75	9.91	0	0.00	1	0.13	74	10.63
	Docetaxel + Sr-89	78	10.30	0	0.00	2	0.26	75	10.78
	Docetaxel + ZA + Sr-89	75	9.91	0	0.00	3	0.40	73	10.49
Bisphosphonate	Docetaxel	42	5.55	2	0.26	11	1.45	31	4.45
	Docetaxel + ZA	40	5.28	0	0.00	26	3.43	24	3.45
	Docetaxel + Sr-89	28	3.70	2	0.26	8	1.06	19	2.73
	Docetaxel + ZA + Sr-89	36	4.76	1	0.13	22	2.91	17	2.44
Hormone therapy	Docetaxel	66	8.72	12	1.59	34	4.49	32	4.60
	Docetaxel + ZA	62	8.19	15	1.98	33	4.36	28	4.02
	Docetaxel + Sr-89	68	8.98	14	1.85	33	4.36	31	4.45
	Docetaxel + ZA + Sr-89	67	8.85	19	2.51	36	4.76	23	3.30
NSAID	Docetaxel	18	2.38	10	1.32	7	0.92	1	0.14
	Docetaxel + ZA	12	1.59	3	0.40	8	1.06	1	0.14
	Docetaxel + Sr-89	14	1.85	3	0.40	6	0.79	1	0.14
	Docetaxel + ZA + Sr-89	12	1.59	3	0.40	6	0.79	2	0.29
ARB	Docetaxel	1	0.13	0	0.00	0	0.00	0	0.00
	Docetaxel + ZA	1	0.13	0	0.00	0	0.00	0	0.00
	Docetaxel + Sr-89	2	0.26	0	0.00	1	0.13	0	0.00
	Docetaxel + ZA + Sr-89	1	0.13	0	0.00	0	0.00	0	0.00
Radioisotope	Docetaxel	11	1.45	0	0.00	0	0.00	11	1.58
	Docetaxel + ZA	11	1.45	0	0.00	1	0.13	10	1.44
	Docetaxel + Sr-89	11	1.45	1	0.13	3	0.40	8	1.15
	Docetaxel + ZA + Sr-89	8	1.06	0	0.00	3	0.40	5	0.72

continued

TABLE 83 Number of patients taking concomitant medications by randomisation arms (*continued*)

Concomitant medications	Arm	Patients	%	On-study	%	Pre-CPFS	%	Post-CPFS	%
GCSF	Docetaxel	9	1.19	0	0.00	7	0.92	1	0.14
	Docetaxel + ZA	6	0.79	0	0.00	6	0.79	0	0.00
	Docetaxel + Sr-89	5	0.66	0	0.00	5	0.66	0	0.00
	Docetaxel + ZA + Sr-89	5	0.66	0	0.00	4	0.53	0	0.00
i.v. fluids for rehydration	Docetaxel + ZA	1	0.13	0	0.00	1	0.13	0	0.00
	Docetaxel + Sr-89	2	0.26	0	0.00	2	0.26	0	0.00
	Docetaxel + ZA + Sr-89	2	0.26	0	0.00	2	0.26	0	0.00
Treatment for glaucoma	Docetaxel	2	0.26	0	0.00	2	0.26	0	0.00
	Docetaxel + ZA	3	0.40	2	0.26	1	0.13	0	0.00
	Docetaxel + Sr-89	1	0.13	1	0.13	0	0.00	0	0.00
	Docetaxel + ZA + Sr-89	5	0.66	4	0.53	2	0.26	0	0.00
Topical anti-inflammatory	Docetaxel	2	0.26	0	0.00	2	0.26	0	0.00
	Docetaxel + ZA	5	0.66	2	0.26	3	0.40	0	0.00
	Docetaxel + Sr-89	1	0.13	0	0.00	0	0.00	0	0.00
	Docetaxel + ZA + Sr-89	1	0.13	0	0.00	0	0.00	1	0.14
Anticonvulsant	Docetaxel	4	0.53	3	0.40	1	0.13	0	0.00
	Docetaxel + ZA	5	0.66	2	0.26	2	0.26	2	0.29
	Docetaxel + Sr-89	10	1.32	4	0.53	3	0.40	3	0.43
	Docetaxel + ZA + Sr-89	4	0.53	2	0.26	0	0.00	2	0.29
Other	Docetaxel	32	4.23	10	1.32	20	2.64	3	0.43
	Docetaxel + ZA	47	6.21	16	2.11	26	3.43	7	1.01
	Docetaxel + Sr-89	46	6.08	14	1.85	20	2.64	9	1.29
	Docetaxel + ZA + Sr-89	40	5.28	18	2.38	24	3.17	3	0.43

ACE, angiotensin-converting-enzyme; ARB, angiotensin receptor blockers; CNS, central nervous system; COX-2, cyclo-oxygenase-2; GCSF, granulocyte colony-sttimulating factor; GI, gastrointestinal; i.v., intravenous; NSAID, non-steroidal anti-inflammatory drug.

TABLE 84 Number of instances of concomitant medications by randomisation arm

Concomitant medications	Arm	Instances	On-study	%	Pre-CPFS	%	Post-CPFS	%
Antacids and simeticone (GI)	Docetaxel	9	2	22.22	5	55.56	2	22.22
	Docetaxel + ZA	8	2	25.00	6	75.00	0	0.00
	Docetaxel + Sr-89	8	1	12.50	6	75.00	0	0.00
	Docetaxel + ZA + Sr-89	21	1	4.76	13	61.90	7	33.33
Antispasmodics	Docetaxel	6	2	33.33	3	50.00	1	16.67
	Docetaxel + ZA	2	1	50.00	1	50.00	0	0.00
	Docetaxel + Sr-89	6	0	0.00	6	100.00	0	0.00
	Docetaxel + ZA + Sr-89	3	2	66.67	1	33.33	0	0.00
H2 antagonist and ulcer healing (GI)	Docetaxel	11	4	36.36	0	0.00	6	54.55
	Docetaxel + ZA	4	3	75.00	1	25.00	0	0.00
	Docetaxel + Sr-89	3	2	66.67	1	33.33	0	0.00
	Docetaxel + ZA + Sr-89	11	8	72.73	1	9.09	1	9.09
Proton pump inhibitors (GI)	Docetaxel	96	58	60.42	31	32.29	5	5.21
	Docetaxel + ZA	98	60	61.22	25	25.51	5	5.10
	Docetaxel + Sr-89	98	48	48.98	34	34.69	9	9.18
	Docetaxel + ZA + Sr-89	90	54	60.00	28	31.11	4	4.44
Antimotility, antidiarrhoea (GI)	Docetaxel	27	1	3.70	24	88.89	2	7.41
	Docetaxel + ZA	11	2	18.18	8	72.73	0	0.00
	Docetaxel + Sr-89	16	1	6.25	14	87.50	0	0.00
	Docetaxel + ZA + Sr-89	7	1	14.29	5	71.43	1	14.29

continued

TABLE 84 Number of instances of concomitant medications by randomisation arm (*continued*)

Concomitant medications	Arm	Instances	On-study	%	Pre-CPFS	%	Post-CPFS	%
Laxatives (GI)	Docetaxel	58	32	55.17	15	25.86	9	15.52
	Docetaxel + ZA	92	51	55.43	30	32.61	3	3.26
	Docetaxel + Sr-89	98	32	32.65	42	42.86	17	17.35
	Docetaxel + ZA + Sr-89	77	37	48.05	28	36.36	8	10.39
Cardiac glycoside (cardiac)	Docetaxel	3	2	66.67	1	33.33	0	0.00
	Docetaxel + ZA	14	12	85.71	2	14.29	0	0.00
	Docetaxel + Sr-89	2	2	100.00	0	0.00	0	0.00
	Docetaxel + ZA + Sr-89	6	5	83.33	0	0.00	0	0.00
Diuretics (cardiac)	Docetaxel	48	27	56.25	15	31.25	4	8.33
	Docetaxel + ZA	56	34	60.71	19	33.93	0	0.00
	Docetaxel + Sr-89	55	28	50.91	19	34.55	5	9.09
	Docetaxel + ZA + Sr-89	43	29	67.44	12	27.91	0	0.00
Drugs for arrhythmias (cardiac)	Docetaxel	4	1	25.00	2	50.00	0	0.00
	Docetaxel + ZA	1	1	100.00	0	0.00	0	0.00
	Docetaxel + Sr-89	7	2	28.57	5	71.43	0	0.00
	Docetaxel + ZA + Sr-89	3	0	0.00	3	100.00	0	0.00
Beta-blockers (cardiac)	Docetaxel	20	16	80.00	1	5.00	1	5.00
	Docetaxel + ZA	32	27	84.38	1	3.13	0	0.00
	Docetaxel + Sr-89	30	27	90.00	2	6.67	1	3.33
	Docetaxel + ZA + Sr-89	38	30	78.95	6	15.79	0	0.00

Concomitant medications	Arm	Instances	On-study	%	Pre-CPFS	%	Post-CPFS	%
Calcium – channel blockers (cardiac)	Docetaxel	27	23	85.19	4	14.81	0	0.00
	Docetaxel + ZA	28	23	82.14	1	3.57	1	3.57
	Docetaxel + Sr-89	34	26	76.47	7	20.59	1	2.94
	Docetaxel + ZA + Sr-89	28	26	92.86	2	7.14	0	0.00
Cardiac – other	Docetaxel	15	11	73.33	3	20.00	0	0.00
	Docetaxel + ZA	26	25	96.15	0	0.00	0	0.00
	Docetaxel + Sr-89	20	19	95.00	1	5.00	1	5.00
	Docetaxel + ZA + Sr-89	24	23	95.83	1	4.17	0	0.00
Anticoagulants antiplatelet drugs	Docetaxel	99	46	46.46	42	42.42	8	8.08
	Docetaxel + ZA	103	44	42.72	48	46.60	4	3.88
	Docetaxel + Sr-89	110	49	44.55	37	33.64	21	19.09
	Docetaxel + ZA + Sr-89	98	49	50.00	41	41.84	6	6.12
Blood bone marrow disorders	Docetaxel	84	10	11.90	58	69.05	14	16.67
	Docetaxel + ZA	53	3	5.66	36	67.92	13	24.53
	Docetaxel + Sr-89	56	3	5.36	41	73.21	10	17.86
	Docetaxel + ZA + Sr-89	63	3	4.76	38	60.32	17	26.98
Bronchodilators antihistamines	Docetaxel	48	15	31.25	23	47.92	8	16.67
	Docetaxel + ZA	42	11	26.19	26	61.90	3	7.14
	Docetaxel + Sr-89	53	22	41.51	22	41.51	6	11.32
	Docetaxel + ZA + Sr-89	59	16	27.12	29	49.15	14	23.73

continued

TABLE 84 Number of instances of concomitant medications by randomisation arm (*continued*)

Concomitant medications	Arm	Instances	On-study	%	Pre-CPFS	%	Post-CPFS	%
Hypnotics (CNS)	Docetaxel	13	6	46.15	3	23.08	2	15.38
	Docetaxel + ZA	6	2	33.33	4	66.67	0	0.00
	Docetaxel + Sr-89	15	8	53.33	4	26.67	1	6.67
	Docetaxel + ZA + Sr-89	11	4	36.36	5	45.45	2	18.18
Anxiolytics (CNS)	Docetaxel	5	2	40.00	0	0.00	3	60.00
	Docetaxel + ZA	3	1	33.33	1	33.33	1	33.33
	Docetaxel + Sr-89	4	1	25.00	3	75.00	0	0.00
	Docetaxel + ZA + Sr-89	4	1	25.00	3	75.00	0	0.00
Antiemetics	Docetaxel	351	17	4.84	312	88.89	20	5.70
	Docetaxel + ZA	367	15	4.09	320	87.19	28	7.63
	Docetaxel + Sr-89	290	7	2.41	261	90.00	21	7.24
	Docetaxel + ZA + Sr-89	335	14	4.18	269	80.30	52	15.52
Central nervous – other	Docetaxel	1	1	100.00	0	0.00	0	0.00
Antibacterials, antifungals and antiviral	Docetaxel	297	17	5.72	242	81.48	32	10.77
	Docetaxel + ZA	292	13	4.45	235	80.48	37	12.67
	Docetaxel + Sr-89	349	16	4.58	290	83.09	40	11.46
	Docetaxel + ZA + Sr-89	238	12	5.04	203	85.29	16	6.72
Diabetes drugs	Docetaxel	20	18	90.00	2	10.00	0	0.00
	Docetaxel + ZA	23	19	82.61	3	13.04	0	0.00
	Docetaxel + Sr-89	22	10	45.45	10	45.45	1	4.55
	Docetaxel + ZA + Sr-89	22	20	90.91	1	4.55	1	4.55

Concomitant medications	Arm	Instances	On-study	%	Pre-CPFS	%	Post-CPFS	%
Nitrate	Docetaxel	16	13	81.25	2	12.50	1	6.25
	Docetaxel + ZA	18	14	77.78	3	16.67	0	0.00
	Docetaxel + Sr-89	22	14	63.64	3	13.64	1	4.55
	Docetaxel + ZA + Sr-89	12	9	75.00	2	16.67	0	0.00
ACE inhibitor	Docetaxel	37	29	78.38	6	16.22	1	2.70
	Docetaxel + ZA	31	23	74.19	5	16.13	1	3.23
	Docetaxel + Sr-89	33	24	72.73	6	18.18	0	0.00
	Docetaxel + ZA + Sr-89	45	34	75.56	7	15.56	1	2.22
Chemotherapy	Docetaxel	76	0	0.00	30	39.47	46	60.53
	Docetaxel + ZA	102	0	0.00	31	30.39	71	69.61
	Docetaxel + Sr-89	110	0	0.00	33	30.00	77	70.00
	Docetaxel + ZA + Sr-89	96	0	0.00	42	43.75	54	56.25
Statin	Docetaxel	50	40	80.00	7	14.00	0	0.00
	Docetaxel + ZA	54	44	81.48	4	7.41	1	1.85
	Docetaxel + Sr-89	57	50	87.72	6	10.53	1	1.75
	Docetaxel + ZA + Sr-89	51	45	88.24	3	5.88	1	1.96
Antidepressant	Docetaxel	25	18	72.00	6	24.00	1	4.00
	Docetaxel + ZA	14	8	57.14	4	28.57	1	7.14
	Docetaxel + Sr-89	25	19	76.00	4	16.00	1	4.00
	Docetaxel + ZA + Sr-89	20	12	60.00	2	10.00	4	20.00

continued

TABLE 84 Number of instances of concomitant medications by randomisation arm (*continued*)

Concomitant medications	Arm	Instances	On-study	%	Pre-CPFS	%	Post-CPFS	%
Alpha blocker	Docetaxel	29	19	65.52	6	20.69	2	6.90
	Docetaxel + ZA	24	15	62.50	5	20.83	1	4.17
	Docetaxel + Sr-89	41	27	65.85	12	29.27	0	0.00
	Docetaxel + ZA + Sr-89	35	23	65.71	11	31.43	0	0.00
COX-2 selective inhibitor	Docetaxel	1	0	0.00	1	100.00	0	0.00
Steroid	Docetaxel	361	22	6.09	274	75.90	63	17.45
	Docetaxel + ZA	329	19	5.78	256	77.81	52	15.81
	Docetaxel + Sr-89	341	14	4.11	262	76.83	63	18.48
	Docetaxel + ZA + Sr-89	363	23	6.34	260	71.63	79	21.76
Supplement	Docetaxel	29	21	72.41	6	20.69	1	3.45
	Docetaxel + ZA	117	22	18.80	68	58.12	13	11.11
	Docetaxel + Sr-89	42	18	42.86	18	42.86	7	16.67
	Docetaxel + ZA + Sr-89	84	20	23.81	57	67.86	4	4.76
Enzyme inhibitor	Docetaxel + ZA	1	0	0.00	0	0.00	1	100.00
Immunosuppressive	Docetaxel + ZA	3	1	33.33	2	66.67	0	0.00
	Docetaxel + ZA + Sr-89	1	1	100.00	0	0.00	0	0.00
Radiotherapy	Docetaxel	101	0	0.00	5	4.95	95	94.06
	Docetaxel + ZA	75	0	0.00	1	1.33	74	98.67
	Docetaxel + Sr-89	81	0	0.00	2	2.47	78	96.30
	Docetaxel + ZA + Sr-89	85	0	0.00	3	3.53	82	96.47
Bisphosphonate	Docetaxel	70	2	2.86	13	18.57	55	78.57
	Docetaxel + ZA	167	0	0.00	47	28.14	120	71.86
	Docetaxel + Sr-89	63	3	4.76	8	12.70	52	82.54
	Docetaxel + ZA + Sr-89	115	1	0.87	32	27.83	82	71.30

Concomitant medications	Arm	Instances	On-study	%	Pre-CPFS	%	Post-CPFS	%
Hormone therapy	Docetaxel	100	12	12.00	46	46.00	40	40.00
	Docetaxel + ZA	96	17	17.71	43	44.79	33	34.38
	Docetaxel + Sr-89	109	14	12.84	47	43.12	46	42.20
	Docetaxel + ZA + Sr-89	106	20	18.87	52	49.06	31	29.25
NSAID	Docetaxel	23	10	43.48	11	47.83	1	4.35
	Docetaxel + ZA	17	3	17.65	12	70.59	1	5.88
	Docetaxel + Sr-89	16	3	18.75	6	37.50	1	6.25
	Docetaxel + ZA + Sr-89	13	3	23.08	6	46.15	2	15.38
ARB	Docetaxel	1	0	0.00	0	0.00	0	0.00
	Docetaxel + ZA	2	0	0.00	0	0.00	0	0.00
	Docetaxel + Sr-89	2	0	0.00	1	50.00	0	0.00
	Docetaxel + ZA + Sr-89	1	0	0.00	0	0.00	0	0.00
Radioisotope	Docetaxel	13	0	0.00	0	0.00	13	100.00
	Docetaxel + ZA	11	0	0.00	1	9.09	10	90.91
	Docetaxel + Sr-89	14	1	7.14	4	28.57	10	71.43
	Docetaxel + ZA + Sr-89	9	0	0.00	3	33.33	6	66.67
GCSF	Docetaxel	11	0	0.00	8	72.73	1	9.09
	Docetaxel + ZA	6	0	0.00	6	100.00	0	0.00
	Docetaxel + Sr-89	5	0	0.00	5	100.00	0	0.00
	Docetaxel + ZA + Sr-89	7	0	0.00	5	71.43	0	0.00

continued

TABLE 84 Number of instances of concomitant medications by randomisation arm (*continued*)

Concomitant medications	Arm	Instances	On-study	%	Pre-CPFS	%	Post-CPFS	%
i.v. fluids for rehydration	Docetaxel + ZA	1	0	0.00	1	100.00	0	0.00
	Docetaxel + Sr-89	5	0	0.00	5	100.00	0	0.00
	Docetaxel + ZA + Sr-89	3	0	0.00	3	100.00	0	0.00
Treatment for glaucoma	Docetaxel	3	0	0.00	3	100.00	0	0.00
	Docetaxel + ZA	4	2	50.00	2	50.00	0	0.00
	Docetaxel + Sr-89	3	3	100.00	0	0.00	0	0.00
	Docetaxel + ZA + Sr-89	9	4	44.44	5	55.56	0	0.00
Topical anti-inflammatory	Docetaxel	2	0	0.00	2	100.00	0	0.00
	Docetaxel + ZA	6	2	33.33	4	66.67	0	0.00
	Docetaxel + Sr-89	1	0	0.00	0	0.00	0	0.00
	Docetaxel + ZA + Sr-89	2	0	0.00	0	0.00	2	100.00
Anticonvulsant	Docetaxel	4	3	75.00	1	25.00	0	0.00
	Docetaxel + ZA	14	2	14.29	8	57.14	4	28.57
	Docetaxel + Sr-89	10	4	40.00	3	30.00	3	30.00
	Docetaxel + ZA + Sr-89	4	2	50.00	0	0.00	2	50.00
Other	Docetaxel	41	12	29.27	25	60.98	3	7.32
	Docetaxel + ZA	65	18	27.69	34	52.31	8	12.31
	Docetaxel + Sr-89	56	15	26.79	24	42.86	9	16.07
	Docetaxel + ZA + Sr-89	56	21	37.50	30	53.57	3	5.36

ACE, angiotensin-converting-enzyme; ARB, angiotensin receptor blockers; CNS, central nervous system; COX-2, cyclo-oxygenase-2; GCSF, granulocyte colony-stimulating factor; GI, gastrointestinal; i.v., intravenous; NSAID, non-steroidal anti-inflammatory drug.

TABLE 85 Number of patients taking concomitant medications by ZA comparison

Concomitant medications	ZA	Patients	%	On-study	%	Pre-CPFS	%	Post-CPFS	%
Antacids and Simeticone	No ZA	15	1.98	3	0.40	10	1.32	2	0.29
	ZA	14	1.85	3	0.40	9	1.19	2	0.29
Antispasmodics	No ZA	8	1.06	2	0.26	5	0.66	1	0.14
	ZA	5	0.66	3	0.40	2	0.26	0	0.00
H2 antagonist and ulcer healing (GI)	No ZA	8	1.06	6	0.79	1	0.13	1	0.14
	ZA	14	1.85	11	1.45	2	0.26	1	0.14
Proton pump inhibitors	No ZA	157	20.74	103	13.61	52	6.87	13	1.87
	ZA	158	20.87	112	14.80	47	6.21	8	1.15
Antimotility, antidiarrhoea	No ZA	36	4.76	2	0.26	31	4.10	2	0.29
	ZA	16	2.11	3	0.40	11	1.45	1	0.14
Laxatives	No ZA	88	11.62	50	6.61	30	3.96	14	2.01
	ZA	107	14.13	71	9.38	34	4.49	10	1.44
Cardiac glycoside	No ZA	4	0.53	4	0.53	1	0.13	0	0.00
	ZA	19	2.51	17	2.25	2	0.26	0	0.00
Diuretics (cardiac)	No ZA	73	9.64	52	6.87	20	2.64	9	1.29
	ZA	79	10.44	60	7.93	24	3.17	0	0.00
Drugs for arrhythmias (cardiac)	No ZA	8	1.06	2	0.26	5	0.66	0	0.00
	ZA	2	0.26	1	0.13	1	0.13	0	0.00
Beta-blockers (cardiac)	No ZA	47	6.21	43	5.68	3	0.40	2	0.29
	ZA	62	8.19	55	7.27	7	0.92	0	0.00

continued

TABLE 85 Number of patients taking concomitant medications by ZA comparison (*continued*)

Concomitant medications	ZA	Patients	%	On-study	%	Pre-CPFS	%	Post-CPFS	%
Calcium-channel blockers (cardiac)	No ZA	53	7.00	48	6.34	9	1.19	1	0.14
	ZA	52	6.87	49	6.47	3	0.40	1	0.14
Cardiac – other	No ZA	32	4.23	29	3.83	4	0.53	1	0.14
	ZA	46	6.08	45	5.94	1	0.13	0	0.00
Anticoagulants antiplatelet drugs	No ZA	138	18.23	90	11.89	48	6.34	16	2.30
	ZA	132	17.44	88	11.62	53	7.00	9	1.29
Blood bone marrow disorders	No ZA	66	8.72	11	1.45	44	5.81	11	1.58
	ZA	54	7.13	6	0.79	40	5.28	11	1.58
Bronchodilators antihistamines	No ZA	53	7.00	26	3.43	25	3.30	9	1.29
	ZA	58	7.66	24	3.17	30	3.96	6	0.86
Hypnotics (CNS)	No ZA	22	2.91	14	1.85	5	0.66	3	0.43
	ZA	15	1.98	6	0.79	7	0.92	2	0.29
Anxiolytics (CNS)	No ZA	8	1.06	3	0.40	3	0.40	2	0.29
	ZA	7	0.92	2	0.26	4	0.53	1	0.14
Antiemetics	No ZA	121	15.98	20	2.64	95	12.55	18	2.59
	ZA	136	17.97	28	3.70	104	13.74	28	4.02
Central nervous – other	No ZA	1	0.13	1	0.13	0	0.00	0	0.00
Antibacterials, antifungals and antiviral	No ZA	201	26.55	29	3.83	178	23.51	28	4.02
	ZA	171	22.59	20	2.64	150	19.82	22	3.16
Diabetes drugs	No ZA	29	3.83	20	2.64	9	1.19	1	0.14
	ZA	31	4.10	27	3.57	4	0.53	1	0.14
Nitrate	No ZA	30	3.96	24	3.17	5	0.66	2	0.29
	ZA	26	3.43	23	3.04	4	0.53	0	0.00

Concomitant medications	ZA	Patients	%	On-study	%	Pre-CPFS	%	Post-CPFS	%
ACE inhibitor	No ZA	59	7.79	52	6.87	7	0.92	1	0.14
	ZA	63	8.32	57	7.53	10	1.32	2	0.29
Chemotherapy	No ZA	69	9.11	0	0.00	34	4.49	37	5.32
	ZA	74	9.78	0	0.00	35	4.62	42	6.03
Statin	No ZA	97	12.81	89	11.76	13	1.72	1	0.14
	ZA	94	12.42	89	11.76	6	0.79	2	0.29
Antidepressant	No ZA	42	5.55	35	4.62	9	1.19	2	0.29
	ZA	29	3.83	19	2.51	5	0.66	5	0.72
Alpha Blocker	No ZA	54	7.13	45	5.94	15	1.98	2	0.29
	ZA	46	6.08	37	4.89	15	1.98	1	0.14
COX-2 selective inhibitor	No ZA	1	0.13	0	0.00	1	0.13	0	0.00
Steroid	No ZA	164	21.66	33	4.36	104	13.74	60	8.62
	ZA	165	21.80	41	5.42	112	14.80	48	6.90
Supplement	No ZA	44	5.81	25	3.30	16	2.11	6	0.86
	ZA	96	12.68	29	3.83	66	8.72	8	1.15
Enzyme inhibitor	ZA	1	0.13	0	0.00	0	0.00	1	0.14
Immunosuppressive	ZA	2	0.26	2	0.26	1	0.13	0	0.00
Radiotherapy	No ZA	165	21.80	0	0.00	7	0.92	157	22.56
	ZA	150	19.82	0	0.00	4	0.53	147	21.12
Bisphosphonate	No ZA	70	9.25	4	0.53	19	2.51	50	7.18
	ZA	76	10.04	1	0.13	48	6.34	41	5.89
Hormone Therapy	No ZA	134	17.70	26	3.43	67	8.85	63	9.05
	ZA	129	17.04	34	4.49	69	9.11	51	7.33

continued

TABLE 85 Number of patients taking concomitant medications by ZA comparison (*continued*)

Concomitant medications	ZA	Patients	%	On-study	%	Pre-CPFS	%	Post-CPFS	%
NSAID	No ZA	32	4.23	13	1.72	13	1.72	2	0.29
	ZA	24	3.17	6	0.79	14	1.85	3	0.43
ARB	No ZA	3	0.40	0	0.00	1	0.13	0	0.00
	ZA	2	0.26	0	0.00	0	0.00	0	0.00
Radioisotope	No ZA	22	2.91	1	0.13	3	0.40	19	2.73
	ZA	19	2.51	0	0.00	4	0.53	15	2.16
GCSF	No ZA	14	1.85	0	0.00	12	1.59	1	0.14
	ZA	11	1.45	0	0.00	10	1.32	0	0.00
i.v. Fluids for Rehydration	No ZA	2	0.26	0	0.00	2	0.26	0	0.00
	ZA	3	0.40	0	0.00	3	0.40	0	0.00
Treatment for glaucoma	No ZA	3	0.40	1	0.13	2	0.26	0	0.00
	ZA	8	1.06	6	0.79	3	0.40	0	0.00
Topical anti-inflammatory	No ZA	3	0.40	0	0.00	2	0.26	0	0.00
	ZA	6	0.79	2	0.26	3	0.40	1	0.14
Anticonvulsant	No ZA	14	1.85	7	0.92	4	0.53	3	0.43
	ZA	9	1.19	4	0.53	2	0.26	4	0.57
Other	No ZA	78	10.30	24	3.17	40	5.28	12	1.72
	ZA	87	11.49	34	4.49	50	6.61	10	1.44

ACE, angiotensin-converting-enzyme; ARB, angiotensin receptor blockers; CNS, central nervous system; COX-2, cyclo-oxygenase-2; GCSF, granulocyte colony-stimulating factor; GI, gastrointestinal; i.v., intravenous; NSAID, non-steroidal anti-inflammatory drug.

TABLE 86 Number of instances of concomitant medications by ZA comparison

Concomitant medications	ZA	Instances	On-study	%	Pre-CPFS	%	Post-CPFS	%
Antacids and simeticone	No ZA	17	3	17.65	11	64.71	2	11.76
	ZA	29	3	10.34	19	65.52	7	24.14
Antispasmodics	No ZA	12	2	16.67	9	75.00	1	8.33
	ZA	5	3	60.00	2	40.00	0	0.00
H2 antagonist and ulcer healing (GI)	No ZA	14	6	42.86	1	7.14	6	42.86
	ZA	15	11	73.33	2	13.33	1	6.67
Proton pump inhibitors	No ZA	194	106	54.64	65	33.51	14	7.22
	ZA	188	114	60.64	53	28.19	9	4.79
Antimotility, antidiarrhoea	No ZA	43	2	4.65	38	88.37	2	4.65
	ZA	18	3	16.67	13	72.22	1	5.56
Laxatives	No ZA	156	64	41.03	57	36.54	26	16.67
	ZA	169	88	52.07	58	34.32	11	6.51
Cardiac glycoside	No ZA	5	4	80.00	1	20.00	0	0.00
	ZA	20	17	85.00	2	10.00	0	0.00
Diuretics (cardiac)	No ZA	103	55	53.40	34	33.01	9	8.74
	ZA	99	63	63.64	31	31.31	0	0.00
Drugs for arrhythmias (cardiac)	No ZA	11	3	27.27	7	63.64	0	0.00
	ZA	4	1	25.00	3	75.00	0	0.00
Beta-blockers (cardiac)	No ZA	50	43	86.00	3	6.00	2	4.00
	ZA	70	57	81.43	7	10.00	0	0.00
Calcium-channel blockers (cardiac)	No ZA	61	49	80.33	11	18.03	1	1.64
	ZA	56	49	87.50	3	5.36	1	1.79

continued

TABLE 86 Number of instances of concomitant medications by ZA comparison (*continued*)

Concomitant medications	ZA	Instances	On-study	%	Pre-CPFS	%	Post-CPFS	%
Cardiac – other	No ZA	35	30	85.71	4	11.43	1	2.86
	ZA	50	48	96.00	1	2.00	0	0.00
Anticoagulants antiplatelet drugs	No ZA	209	95	45.45	79	37.80	29	13.88
	ZA	201	93	46.27	89	44.28	10	4.98
Blood bone marrow disorders	No ZA	140	13	9.29	99	70.71	24	17.14
	ZA	116	6	5.17	74	63.79	30	25.86
Bronchodilators antihistamines	No ZA	101	37	36.63	45	44.55	14	13.86
	ZA	101	27	26.73	55	54.46	17	16.83
Hypnotics (CNS)	No ZA	28	14	50.00	7	25.00	3	10.71
	ZA	17	6	35.29	9	52.94	2	11.76
Anxiolytics (CNS)	No ZA	9	3	33.33	3	33.33	3	33.33
	ZA	7	2	28.57	4	57.14	1	14.29
Antiemetics	No ZA	641	24	3.74	573	89.39	41	6.40
	ZA	702	29	4.13	589	83.90	80	11.40
Central nervous – other	No ZA	1	1	100.00	0	0.00	0	0.00
Diabetes drugs	No ZA	42	28	66.67	12	28.57	1	2.38
	ZA	45	39	86.67	4	8.89	1	2.22
Nitrate	No ZA	38	27	71.05	5	13.16	2	5.26
	ZA	30	23	76.67	5	16.67	0	0.00
ACE inhibitor	No ZA	70	53	75.71	12	17.14	1	1.43
	ZA	76	57	75.00	12	15.79	2	2.63
Chemotherapy	No ZA	186	0	0.00	63	33.87	123	66.13
	ZA	198	0	0.00	73	36.87	125	63.13

Concomitant medications	ZA	Instances	On-study	%	Pre-CPFS	%	Post-CPFS	%
Statin	No ZA	107	90	84.11	13	12.15	1	0.93
	ZA	105	89	84.76	7	6.67	2	1.90
Antidepressant	No ZA	50	37	74.00	10	20.00	2	4.00
	ZA	34	20	58.82	6	17.65	5	14.71
Alpha blocker	No ZA	70	46	65.71	18	25.71	2	2.86
	ZA	59	38	64.41	16	27.12	1	1.69
COX-2 selective inhibitor	No ZA	1	0	0.00	1	100.00	0	0.00
Steroid	No ZA	702	36	5.13	536	76.35	126	17.95
	ZA	692	42	6.07	516	74.57	131	18.93
Supplement	No ZA	71	39	54.93	24	33.80	8	11.27
	ZA	201	42	20.90	125	62.19	17	8.46
Enzyme inhibitor	ZA	1	0	0.00	0	0.00	1	100.00
Immunosuppressive	ZA	4	2	50.00	2	50.00	0	0.00
Radiotherapy	No ZA	182	0	0.00	7	3.85	173	95.05
	ZA	160	0	0.00	4	2.50	156	97.50
Bisphosphonate	No ZA	133	5	3.76	21	15.79	107	80.45
	ZA	282	1	0.35	79	28.01	202	71.63
Hormone therapy	No ZA	209	26	12.44	93	44.50	86	41.15
	ZA	202	37	18.32	95	47.03	64	31.68
NSAID	No ZA	39	13	33.33	17	43.59	2	5.13
	ZA	30	6	20.00	18	60.00	3	10.00
ARB	No ZA	3	0	0.00	1	33.33	0	0.00

continued

TABLE 86 Number of instances of concomitant medications by ZA comparison (*continued*)

Concomitant medications	ZA	Instances	On-study	%	Pre-CPFS	%	Post-CPFS	%
	ZA	3	0	0.00	0	0.00	0	0.00
Radioisotope	No ZA	27	1	3.70	4	14.81	23	85.19
	ZA	20	0	0.00	4	20.00	16	80.00
GCSF	No ZA	16	0	0.00	13	81.25	1	6.25
	ZA	13	0	0.00	11	84.62	0	0.00
i.v. fluids for rehydration	No ZA	5	0	0.00	5	100.00	0	0.00
	ZA	4	0	0.00	4	100.00	0	0.00
Treatment for glaucoma	No ZA	6	3	50.00	3	50.00	0	0.00
	ZA	13	6	46.15	7	53.85	0	0.00
Topical anti-inflammatory	No ZA	3	0	0.00	2	66.67	0	0.00
	ZA	8	2	25.00	4	50.00	2	25.00
Anticonvulsant	No ZA	14	7	50.00	4	28.57	3	21.43
	ZA	18	4	22.22	8	44.44	6	33.33
Other	No ZA	97	27	27.84	49	50.52	12	12.37
	ZA	121	39	32.23	64	52.89	11	9.09

ACE, angiotensin-converting-enzyme; ARB, angiotensin receptor blockers; CNS, central nervous system; COX-2, cyclo-oxygenase-2; GCSF, granulocyte colony-stimulating factor; GI, gastrointestinal; i.v., intravenous; NSAID, non-steroidal anti-inflammatory drug.

TABLE 87 Number of patients taking concomitant medications by Sr-89 comparison

Concomitant medications	Sr-89	Patients	%	On-study	%	Pre-CPFS	%	Post-CPFS	%
Antacids and simeticone	No Sr-89	13	1.72	4	0.53	8	1.06	2	0.29
	Sr-89	16	2.11	2	0.26	11	1.45	2	0.29
Antispasmodics	No Sr-89	8	1.06	3	0.40	4	0.53	1	0.14
	Sr-89	5	0.66	2	0.26	3	0.40	0	0.00
H2 antagonist and ulcer healing (GI)	No Sr-89	10	1.32	7	0.92	1	0.13	1	0.14
	Sr-89	12	1.59	10	1.32	2	0.26	1	0.14
Proton pump inhibitors	No Sr-89	166	21.93	116	15.32	49	6.47	9	1.29
	Sr-89	149	19.68	99	13.08	50	6.61	12	1.72
Antimotility, antidiarrhoea	No Sr-89	31	4.10	3	0.40	25	3.30	2	0.29
	Sr-89	21	2.77	2	0.26	17	2.25	1	0.14
Laxatives	No Sr-89	97	12.81	67	8.85	30	3.96	8	1.15
	Sr-89	98	12.95	54	7.13	34	4.49	16	2.30
Cardiac glycoside	No Sr-89	15	1.98	14	1.85	3	0.40	0	0.00
	Sr-89	8	1.06	7	0.92	0	0.00	0	0.00
Diuretics (cardiac)	No Sr-89	81	10.70	58	7.66	26	3.43	4	0.57
	Sr-89	71	9.38	54	7.13	18	2.38	5	0.72
Drugs for arrhythmias (cardiac)	No Sr-89	5	0.66	2	0.26	2	0.26	0	0.00
	Sr-89	5	0.66	1	0.13	4	0.53	0	0.00
Beta-blockers (cardiac)	No Sr-89	47	6.21	42	5.55	2	0.26	1	0.14
	Sr-89	62	8.19	56	7.40	8	1.06	1	0.14
Calcium-channel blockers (cardiac)	No Sr-89	51	6.74	46	6.08	5	0.66	1	0.14
	Sr-89	54	7.13	51	6.74	7	0.92	1	0.14

continued

TABLE 87 Number of patients taking concomitant medications by Sr-89 comparison (*continued*)

Concomitant medications	Sr-89	Patients	%	On-study	%	Pre-CPFS	%	Post-CPFS	%
Cardiac – other	No Sr-89	37	4.89	34	4.49	3	0.40	0	0.00
	Sr-89	41	5.42	40	5.28	2	0.26	1	0.14
Anticoagulants antiplatelet drugs	No Sr-89	135	17.83	88	11.62	53	7.00	9	1.29
	Sr-89	135	17.83	90	11.89	48	6.34	16	2.30
Blood bone marrow disorders	No Sr-89	62	8.19	11	1.45	45	5.94	11	1.58
	Sr-89	58	7.66	6	0.79	39	5.15	11	1.58
Bronchodilators antihistamines	No Sr-89	53	7.00	21	2.77	28	3.70	5	0.72
	Sr-89	58	7.66	29	3.83	27	3.57	10	1.44
Hypnotics (CNS)	No Sr-89	17	2.25	8	1.06	7	0.92	2	0.29
	Sr-89	20	2.64	12	1.59	5	0.66	3	0.43
Anxiolytics (CNS)	No Sr-89	7	0.92	3	0.40	1	0.13	3	0.43
	Sr-89	8	1.06	2	0.26	6	0.79	0	0.00
Antiemetics	No Sr-89	133	17.57	28	3.70	105	13.87	19	2.73
	Sr-89	124	16.38	20	2.64	94	12.42	27	3.88
Central nervous – other	No Sr-89	1	0.13	1	0.13	0	0.00	0	0.00
Diabetes drugs	No Sr-89	29	3.83	25	3.30	5	0.66	0	0.00
	Sr-89	31	4.10	22	2.91	8	1.06	2	0.29
Nitrate	No Sr-89	28	3.70	25	3.30	4	0.53	1	0.14
	Sr-89	28	3.70	22	2.91	5	0.66	1	0.14
ACE inhibitor	No Sr-89	61	8.06	52	6.87	9	1.19	2	0.29
	Sr-89	61	8.06	57	7.53	8	1.06	1	0.14
Chemotherapy	No Sr-89	64	8.45	0	0.00	34	4.49	34	4.89
	Sr-89	79	10.44	0	0.00	35	4.62	45	6.47

Concomitant medications	Sr-89	Patients	%	On-study	%	Pre-CPFS	%	Post-CPFS	%
Statin	No Sr-89	93	12.29	84	11.10	10	1.32	1	0.14
	Sr-89	98	12.95	94	12.42	9	1.19	2	0.29
Antidepressant	No Sr-89	35	4.62	26	3.43	9	1.19	2	0.29
	Sr-89	36	4.76	28	3.70	5	0.66	5	0.72
Alpha-blocker	No Sr-89	43	5.68	34	4.49	10	1.32	3	0.43
	Sr-89	57	7.53	48	6.34	20	2.64	0	0.00
COX-2 selective inhibitor	No Sr-89	1	0.13	0	0.00	1	0.13	0	0.00
Steroid	No Sr-89	177	23.38	37	4.89	118	15.59	52	7.47
	Sr-89	152	20.08	37	4.89	98	12.95	56	8.05
Supplement	No Sr-89	74	9.78	28	3.70	42	5.55	5	0.72
	Sr-89	66	8.72	26	3.43	40	5.28	9	1.29
Enzyme inhibitor	No Sr-89	1	0.13	0	0.00	0	0.00	1	0.14
Immunosuppressive	No Sr-89	1	0.13	1	0.13	1	0.13	0	0.00
	Sr-89	1	0.13	1	0.13	0	0.00	0	0.00
Radiotherapy	No Sr-89	162	21.40	0	0.00	6	0.79	156	22.41
	Sr-89	153	20.21	0	0.00	5	0.66	148	21.26
Bisphosphonate	No Sr-89	82	10.83	2	0.26	37	4.89	55	7.90
	Sr-89	64	8.45	3	0.40	30	3.96	36	5.17
Hormone therapy	No Sr-89	128	16.91	27	3.57	67	8.85	60	8.62
	Sr-89	135	17.83	33	4.36	69	9.11	54	7.76
NSAID	No Sr-89	30	3.96	13	1.72	15	1.98	2	0.29
	Sr-89	26	3.43	6	0.79	12	1.59	3	0.43

continued

TABLE 87 Number of patients taking concomitant medications by Sr-89 comparison (*continued*)

Concomitant medications	Sr-89	Patients	%	On-study	%	Pre-CPFS	%	Post-CPFS	%
ARB	No Sr-89	2	0.26	0	0.00	0	0.00	0	0.00
	Sr-89	3	0.40	0	0.00	1	0.13	0	0.00
Radioisotope	No Sr-89	22	2.91	0	0.00	1	0.13	21	3.02
	Sr-89	19	2.51	1	0.13	6	0.79	13	1.87
GCSF	No Sr-89	15	1.98	0	0.00	13	1.72	1	0.14
	Sr-89	10	1.32	0	0.00	9	1.19	0	0.00
i.v fluids for rehydration	No Sr-89	1	0.13	0	0.00	1	0.13	0	0.00
	Sr-89	4	0.53	0	0.00	4	0.53	0	0.00
Treatment for glaucoma	No Sr-89	5	0.66	2	0.26	3	0.40	0	0.00
	Sr-89	6	0.79	5	0.66	2	0.26	0	0.00
Topical anti-inflammatory	No Sr-89	7	0.92	2	0.26	5	0.66	0	0.00
	Sr-89	2	0.26	0	0.00	0	0.00	1	0.14
Anticonvulsant	No Sr-89	9	1.19	5	0.66	3	0.40	2	0.29
	Sr-89	14	1.85	6	0.79	3	0.40	5	0.72
Other	No Sr-89	79	10.44	26	3.43	46	6.08	10	1.44
	Sr-89	86	11.36	32	4.23	44	5.81	12	1.72

ACE, angiotensin-converting-enzyme; ARB, angiotensin receptor blockers; CNS, central nervous system; COX-2, cyclo-oxygenase-2; GCSF, granulocyte colony-stimulating factor; GI, gastrointestinal; i.v., intravenous; NSAID, non-steroidal anti-inflammatory drug.

TABLE 88 Number of instances of concomitant medications by Sr-89 comparison

Concomitant medications	Sr-89	Instances	OS	%	Pre-CPFS	%	Post-CPFS	%
Antacids and simeticone	No Sr-89	17	4	23.53	11	64.71	2	11.76
	Sr-89	29	2	6.90	19	65.52	7	24.14
Antispasmodics	No Sr-89	8	3	37.50	4	50.00	1	12.50
	Sr-89	9	2	22.22	7	77.78	0	0.00
H2 antagonist and ulcer healing (GI)	No Sr-89	15	7	46.67	1	6.67	6	40.00
	Sr-89	14	10	71.43	2	14.29	1	7.14
Proton pump inhibitors	No Sr-89	194	118	60.82	56	28.87	10	5.15
	Sr-89	188	102	54.26	62	32.98	13	6.91
Antimotility, antidiarrhoea	No Sr-89	38	3	7.89	32	84.21	2	5.26
	Sr-89	23	2	8.70	19	82.61	1	4.35
Laxatives	No Sr-89	150	83	55.33	45	30.00	12	8.00
	Sr-89	175	69	39.43	70	40.00	25	14.29
Cardiac glycoside	No Sr-89	17	14	82.35	3	17.65	0	0.00
	Sr-89	8	7	87.50	0	0.00	0	0.00
Diuretics (cardiac)	No Sr-89	104	61	58.65	34	32.69	4	3.85
	Sr-89	98	57	58.16	31	31.63	5	5.10
Drugs for arrhythmias (cardiac)	No Sr-89	5	2	40.00	2	40.00	0	0.00
	Sr-89	10	2	20.00	8	80.00	0	0.00
Beta-blockers (cardiac)	No Sr-89	52	43	82.69	2	3.85	1	1.92
	Sr-89	68	57	83.82	8	11.76	1	1.47
Calcium-channel blockers (cardiac)	No Sr-89	55	46	83.64	5	9.09	1	1.82
	Sr-89	62	52	83.87	9	14.52	1	1.61

continued

TABLE 88 Number of instances of concomitant medications by Sr-89 comparison (*continued*)

Concomitant medications	Sr-89	Instances	OS	%	Pre-CPFS	%	Post-CPFS	%
Cardiac – other	No Sr-89	41	36	87.80	3	7.32	0	0.00
	Sr-89	44	42	95.45	2	4.55	1	2.27
Anticoagulants antiplatelet drugs	No Sr-89	202	90	44.55	90	44.55	12	5.94
	Sr-89	208	98	47.12	78	37.50	27	12.98
Blood bone marrow disorders	No Sr-89	137	13	9.49	94	68.61	27	19.71
	Sr-89	119	6	5.04	79	66.39	27	22.69
Bronchodilators antihistamines	No Sr-89	90	26	28.89	49	54.44	11	12.22
	Sr-89	112	38	33.93	51	45.54	20	17.86
Hypnotics (CNS)	No Sr-89	19	8	42.11	7	36.84	2	10.53
	Sr-89	26	12	46.15	9	34.62	3	11.54
Anxiolytics (CNS)	No Sr-89	8	3	37.50	1	12.50	4	50.00
	Sr-89	8	2	25.00	6	75.00	0	0.00
Antiemetics	No Sr-89	718	32	4.46	632	88.02	48	6.69
	Sr-89	625	21	3.36	530	84.80	73	11.68
Central nervous – other	No Sr-89	1	1	100.00	0	0.00	0	0.00
Diabetes drugs	No Sr-89	43	37	86.05	5	11.63	0	0.00
	Sr-89	44	30	68.18	11	25.00	2	4.55
Nitrate	No Sr-89	34	27	79.41	5	14.71	1	2.94
	Sr-89	34	23	67.65	5	14.71	1	2.94
ACE inhibitor	No Sr-89	68	52	76.47	11	16.18	2	2.94
	Sr-89	78	58	74.36	13	16.67	1	1.28
Chemotherapy	No Sr-89	178	0	0.00	61	34.27	117	65.73
	Sr-89	206	0	0.00	75	36.41	131	63.59

Concomitant medications	Sr-89	Instances	OS	%	Pre-CPFS	%	Post-CPFS	%
Statin	No Sr-89	104	84	80.77	11	10.58	1	0.96
	Sr-89	108	95	87.96	9	8.33	2	1.85
Antidepressant	No Sr-89	39	26	66.67	10	25.64	2	5.13
	Sr-89	45	31	68.89	6	13.33	5	11.11
Alpha-blocker	No Sr-89	53	34	64.15	11	20.75	3	5.66
	Sr-89	76	50	65.79	23	30.26	0	0.00
COX-2 selective inhibitor	No Sr-89	1	0	0.00	1	100.00	0	0.00
Steroid	No Sr-89	690	41	5.94	530	76.81	115	16.67
	Sr-89	704	37	5.26	522	74.15	142	20.17
Supplement	No Sr-89	146	43	29.45	74	50.68	14	9.59
	Sr-89	126	38	30.16	75	59.52	11	8.73
Enzyme inhibitor	No Sr-89	1	0	0.00	0	0.00	1	100.00
Immunosuppressive	No Sr-89	3	1	33.33	2	66.67	0	0.00
	Sr-89	1	1	100.00	0	0.00	0	0.00
Radiotherapy	No Sr-89	176	0	0.00	6	3.41	169	96.02
	Sr-89	166	0	0.00	5	3.01	160	96.39
Bisphosphonate	No Sr-89	237	2	0.84	60	25.32	175	73.84
	Sr-89	178	4	2.25	40	22.47	134	75.28
Hormone therapy	No Sr-89	196	29	14.80	89	45.41	73	37.24
	Sr-89	215	34	15.81	99	46.05	77	35.81
NSAID	No Sr-89	40	13	32.50	23	57.50	2	5.00
	Sr-89	29	6	20.69	12	41.38	3	10.34

continued

TABLE 88 Number of instances of concomitant medications by Sr-89 comparison (*continued*)

Concomitant medications	Sr-89	Instances	OS	%	Pre-CPFS	%	Post-CPFS	%
ARB	No Sr-89	3	0	0.00	0	0.00	0	0.00
	Sr-89	3	0	0.00	1	33.33	0	0.00
Radioisotope	No Sr-89	24	0	0.00	1	4.17	23	95.83
	Sr-89	23	1	4.35	7	30.43	16	69.57
GCSF	No Sr-89	17	0	0.00	14	82.35	1	5.88
	Sr-89	12	0	0.00	10	83.33	0	0.00
i.v. fluids for rehydration	No Sr-89	1	0	0.00	1	100.00	0	0.00
	Sr-89	8	0	0.00	8	100.00	0	0.00
Treatment for glaucoma	No Sr-89	7	2	28.57	5	71.43	0	0.00
	Sr-89	12	7	58.33	5	41.67	0	0.00
Topical anti-inflammatory	No Sr-89	8	2	25.00	6	75.00	0	0.00
	Sr-89	3	0	0.00	0	0.00	2	66.67
Anticonvulsant	No Sr-89	18	5	27.78	9	50.00	4	22.22
	Sr-89	14	6	42.86	3	21.43	5	35.71
Other	No Sr-89	106	30	28.30	59	55.66	11	10.38
	Sr-89	112	36	32.14	54	48.21	12	10.71

ACE, angiotensin-converting-enzyme; ARB, angiotensin receptor blockers; CNS, central nervous system; COX-2, cyclo-oxygenase-2; GCSF, granulocyte colony-stimulating factor; GI, gastrointestinal; i.v., intravenous; NSAID, non-steroidal anti-inflammatory drug.

TABLE 89 Number of patients taking analgesic medications by randomisation arms

Analgesic	Arm	Patients	%	On-study	%	Pre-CPFS	%	Post-CPFS	%
Acetaminophen/ paracetamol	Docetaxel	120	15.85	52	6.87	109	14.40	33	4.74
	Docetaxel + ZA	120	15.85	51	6.74	107	14.13	33	4.74
	Docetaxel + Sr-89	118	15.59	55	7.27	105	13.87	32	4.60
	Docetaxel + ZA + Sr-89	116	15.32	50	6.61	105	13.87	32	4.60
Aspirin	Docetaxel	7	0.92	2	0.26	6	0.79	1	0.14
	Docetaxel + ZA	4	0.53	2	0.26	3	0.40	1	0.14
	Docetaxel + Sr-89	7	0.92	1	0.13	6	0.79	2	0.29
	Docetaxel + ZA + Sr-89	4	0.53	0	0.00	4	0.53	2	0.29
Diclofenac	Docetaxel	37	4.89	21	2.77	32	4.23	10	1.44
	Docetaxel + ZA	48	6.34	19	2.51	35	4.62	12	1.72
	Docetaxel + Sr-89	43	5.68	19	2.51	36	4.76	13	1.87
	Docetaxel + ZA + Sr-89	35	4.62	17	2.25	31	4.10	13	1.87
Ibuprofen	Docetaxel	29	3.83	6	0.79	25	3.30	9	1.29
	Docetaxel + ZA	35	4.62	12	1.59	30	3.96	4	0.57
	Docetaxel + Sr-89	34	4.49	12	1.59	29	3.83	7	1.01
	Docetaxel + ZA + Sr-89	38	5.02	18	2.38	31	4.10	8	1.15
Naproxen	Docetaxel	12	1.59	8	1.06	9	1.19	3	0.43
	Docetaxel + ZA	10	1.32	1	0.13	8	1.06	2	0.29
	Docetaxel + Sr-89	8	1.06	2	0.26	6	0.79	2	0.29
	Docetaxel + ZA + Sr-89	6	0.79	2	0.26	5	0.66	2	0.29
Codeine	Docetaxel	55	7.27	20	2.64	48	6.34	10	1.44
	Docetaxel + ZA	60	7.93	25	3.30	49	6.47	11	1.58
	Docetaxel + Sr-89	58	7.66	21	2.77	48	6.34	14	2.01
	Docetaxel + ZA + Sr-89	55	7.27	22	2.91	51	6.74	10	1.44

continued

TABLE 89 Number of patients taking analgesic medications by randomisation arms (*continued*)

Analgesic	Arm	Patients	%	On-study	%	Pre-CPFS	%	Post-CPFS	%
Dihydrocodeine	Docetaxel	16	2.11	7	0.92	13	1.72	2	0.29
	Docetaxel + ZA	10	1.32	5	0.66	9	1.19	3	0.43
	Docetaxel + Sr-89	15	1.98	7	0.92	13	1.72	3	0.43
	Docetaxel + ZA + Sr-89	14	1.85	2	0.26	12	1.59	4	0.57
Morphine	Docetaxel	54	7.13	21	2.77	44	5.81	22	3.16
	Docetaxel + ZA	53	7.00	21	2.77	42	5.55	19	2.73
	Docetaxel + Sr-89	59	7.79	21	2.77	45	5.94	26	3.74
	Docetaxel + ZA + Sr-89	46	6.08	23	3.04	38	5.02	18	2.59
Oxycodone	Docetaxel	16	2.11	5	0.66	10	1.32	7	1.01
	Docetaxel + ZA	21	2.77	4	0.53	13	1.72	11	1.58
	Docetaxel + Sr-89	18	2.38	6	0.79	14	1.85	6	0.86
	Docetaxel + ZA + Sr-89	12	1.59	6	0.79	8	1.06	3	0.43
Tramadol	Docetaxel	29	3.83	11	1.45	25	3.30	5	0.72
	Docetaxel + ZA	22	2.91	10	1.32	18	2.38	2	0.29
	Docetaxel + Sr-89	19	2.51	6	0.79	14	1.85	5	0.72
	Docetaxel + ZA + Sr-89	26	3.43	13	1.72	22	2.91	8	1.15
Fentanyl patch	Docetaxel	7	0.92	3	0.40	6	0.79	4	0.57
	Docetaxel + ZA	10	1.32	3	0.40	9	1.19	7	1.01
	Docetaxel + Sr-89	7	0.92	1	0.13	4	0.53	4	0.57
	Docetaxel + ZA + Sr-89	7	0.92	2	0.26	6	0.79	3	0.43

TABLE 90 Number of instances of analgesic medications by randomisation arms

Analgesic	Arm	Instances	OS	%	Pre-CPFS	%	Post-CPFS	%
Acetaminophen/ paracetamol	Docetaxel	2851	192	6.73	2194	76.96	465	16.31
	Docetaxel + ZA	3090	210	6.80	2309	74.72	571	18.48
	Docetaxel + Sr-89	3120	214	6.86	2466	79.04	440	14.10
	Docetaxel + ZA + Sr-89	3165	214	6.76	2311	73.02	640	20.22
Aspirin	Docetaxel	76	4	5.26	67	88.16	5	6.58
	Docetaxel + ZA	49	9	18.37	26	53.06	14	28.57
	Docetaxel + Sr-89	117	4	3.42	91	77.78	22	18.80
	Docetaxel + ZA + Sr-89	125	0	0.00	73	58.40	52	41.60
Diclofenac	Docetaxel	1209	91	7.53	972	80.40	146	12.08
	Docetaxel + ZA	1097	85	7.75	821	74.84	191	17.41
	Docetaxel + Sr-89	1116	76	6.81	867	77.69	173	15.50
	Docetaxel + ZA + Sr-89	986	68	6.90	773	78.40	144	14.60
Ibuprofen	Docetaxel	665	27	4.06	513	77.14	125	18.80
	Docetaxel + ZA	590	49	8.31	519	87.97	22	3.73
	Docetaxel + Sr-89	551	57	10.34	370	67.15	125	22.69
	Docetaxel + ZA + Sr-89	616	79	12.82	390	63.31	147	23.86
Naproxen	Docetaxel	302	36	11.92	234	77.48	32	10.60
	Docetaxel + ZA	185	2	1.08	163	88.11	20	10.81
	Docetaxel + Sr-89	278	8	2.88	258	92.81	12	4.32
	Docetaxel + ZA + Sr-89	146	14	9.59	101	69.18	31	21.23
Codeine	Docetaxel	1238	70	5.65	999	80.69	169	13.65
	Docetaxel + ZA	1232	87	7.06	944	76.62	201	16.31
	Docetaxel + Sr-89	1139	84	7.37	847	74.36	208	18.26
	Docetaxel + ZA + Sr-89	1106	106	9.58	879	79.48	121	10.94

continued

TABLE 90 Number of instances of analgesic medications by randomisation arms (*continued*)

Analgesic	Arm	Instances	OS	%	Pre-CPFS	%	Post-CPFS	%
Dihydrocodeine	Docetaxel	244	25	10.25	183	75.00	36	14.75
	Docetaxel + ZA	184	27	14.67	112	60.87	45	24.46
	Docetaxel + Sr-89	285	31	10.88	225	78.95	29	10.18
	Docetaxel + ZA + Sr-89	161	3	1.86	137	85.09	21	13.04
Morphine	Docetaxel	2262	144	6.37	1566	69.23	551	24.36
	Docetaxel + ZA	2058	141	6.85	1575	76.53	342	16.62
	Docetaxel + Sr-89	2259	109	4.83	1656	73.31	495	21.91
	Docetaxel + ZA + Sr-89	1740	113	6.49	1211	69.60	416	23.91
Oxycodone	Docetaxel	331	38	11.48	169	51.06	123	37.16
	Docetaxel + ZA	547	6	1.10	370	67.64	169	30.90
	Docetaxel + Sr-89	711	39	5.49	560	78.76	112	15.75
	Docetaxel + ZA + Sr-89	398	33	8.29	282	70.85	83	20.85
Tramadol	Docetaxel	462	49	10.61	388	83.98	25	5.41
	Docetaxel + ZA	276	35	12.68	210	76.09	31	11.23
	Docetaxel + Sr-89	455	30	6.59	331	72.75	94	20.66
	Docetaxel + ZA + Sr-89	765	53	6.93	601	78.56	111	14.51
Fentanyl patch	Docetaxel	172	21	12.21	88	51.16	63	36.63
	Docetaxel + ZA	374	15	4.01	261	69.79	97	25.94
	Docetaxel + Sr-89	116	1	0.86	84	72.41	31	26.72
	Docetaxel + ZA + Sr-89	211	12	5.69	132	62.56	67	31.75

TABLE 91 Number of patients taking analgesic medications by ZA comparison

Analgesic	Treatment	Patients	%	On-study	%	Pre-CPFS	%	Post-CPFS	%
Acetaminophen/ paracetamol	No ZA	238	31.44	107	14.13	214	28.27	65	9.34
	ZA	236	31.18	101	13.34	212	28.01	65	9.34
Aspirin	No ZA	14	1.85	3	0.40	12	1.59	3	0.43
	ZA	8	1.06	2	0.26	7	0.92	3	0.43
Diclofenac	No ZA	80	10.57	40	5.28	68	8.98	23	3.30
	ZA	83	10.96	36	4.76	66	8.72	25	3.59
Ibuprofen	No ZA	63	8.32	18	2.38	54	7.13	16	2.30
	ZA	73	9.64	30	3.96	61	8.06	12	1.72
Naproxen	No ZA	20	2.64	10	1.32	15	1.98	5	0.72
	ZA	16	2.11	3	0.40	13	1.72	4	0.57
Codeine	No ZA	113	14.93	41	5.42	96	12.68	24	3.45
	ZA	115	15.19	47	6.21	100	13.21	21	3.02
Dihydrocodeine	No ZA	31	4.10	14	1.85	26	3.43	5	0.72
	ZA	24	3.17	7	0.92	21	2.77	7	1.01
Morphine	No ZA	113	14.93	42	5.55	89	11.76	48	6.90
	ZA	99	13.08	44	5.81	80	10.57	37	5.32
Oxycodone	No ZA	34	4.49	11	1.45	24	3.17	13	1.87
	ZA	33	4.36	10	1.32	21	2.77	14	2.01
Tramadol	No ZA	48	6.34	17	2.25	39	5.15	10	1.44
	ZA	48	6.34	23	3.04	40	5.28	10	1.44
Fentanyl patch	No ZA	14	1.85	4	0.53	10	1.32	8	1.15
	ZA	17	2.25	5	0.66	15	1.98	10	1.44

TABLE 92 Number of instances of analgesic medications by ZA comparison

Analgesic	Treatment	Instances	OS	%	Pre-CPFS	%	Post-CPFS	%
Acetaminophen/ paracetamol	No ZA	5971	406	6.80	4660	78.04	905	15.16
	ZA	6255	424	6.78	4620	73.86	1211	19.36
Aspirin	No ZA	193	8	4.15	158	81.87	27	13.99
	ZA	174	9	5.17	99	56.90	66	37.93
Diclofenac	No ZA	2325	167	7.18	1839	79.10	319	13.72
	ZA	2083	153	7.35	1594	76.52	335	16.08
Ibuprofen	No ZA	1216	84	6.91	883	72.62	250	20.56
	ZA	1206	128	10.61	909	75.37	169	14.01
Naproxen	No ZA	580	44	7.59	492	84.83	44	7.59
	ZA	331	16	4.83	264	79.76	51	15.41
Codeine	No ZA	2377	154	6.48	1846	77.66	377	15.86
	ZA	2338	193	8.25	1823	77.97	322	13.77
Dihydrocodeine	No ZA	529	56	10.59	408	77.13	65	12.29
	ZA	345	30	8.70	249	72.17	66	19.13
Morphine	No ZA	4521	253	5.60	3222	71.27	1046	23.14
	ZA	3798	254	6.69	2786	73.35	758	19.96
Oxycodone	No ZA	1042	77	7.39	729	69.96	235	22.55
	ZA	945	39	4.13	652	68.99	252	26.67
Tramadol	No ZA	917	79	8.62	719	78.41	119	12.98
	ZA	1041	88	8.45	811	77.91	142	13.64
Fentanyl patch	No ZA	288	22	7.64	172	59.72	94	32.64
	ZA	585	27	4.62	393	67.18	164	28.03

TABLE 93 Number of patients taking analgesic medications by Sr-89 comparison

Analgesic	Treatment	Patients	%	On-study	%	Pre-CPFS	%	Post-CPFS	%
Acetaminophen/ paracetamol	No Sr-89	240	31.70	103	13.61	216	28.53	66	9.48
	Sr-89	234	30.91	105	13.87	210	27.74	64	9.20
Aspirin	No Sr-89	11	1.45	4	0.53	9	1.19	2	0.29
	Sr-89	11	1.45	1	0.13	10	1.32	4	0.57
Celecoxib	No Sr-89	2	0.26	1	0.13	2	0.26	0	0.00
Diclofenac	No Sr-89	85	11.23	40	5.28	67	8.85	22	3.16
	Sr-89	78	10.30	36	4.76	67	8.85	26	3.74
Etodolac	No Sr-89	3	0.40	0	0.00	3	0.40	0	0.00
Flurbiprofen	No Sr-89	1	0.13	0	0.00	0	0.00	1	0.14
Ibuprofen	No Sr-89	64	8.45	18	2.38	55	7.27	13	1.87
	Sr-89	72	9.51	30	3.96	60	7.93	15	2.16
Indomethacin	No Sr-89	1	0.13	0	0.00	1	0.13	0	0.00
	Sr-89	1	0.13	1	0.13	1	0.13	0	0.00
Nabumetone	No Sr-89	1	0.13	1	0.13	1	0.13	0	0.00
Naproxen	No Sr-89	22	2.91	9	1.19	17	2.25	5	0.72
	Sr-89	14	1.85	4	0.53	11	1.45	4	0.57
Buprenorphine	No Sr-89	4	0.53	1	0.13	4	0.53	2	0.29
	Sr-89	5	0.66	0	0.00	3	0.40	2	0.29
Codeine	No Sr-89	115	15.19	45	5.94	97	12.81	21	3.02
	Sr-89	113	14.93	43	5.68	99	13.08	24	3.45
Dextropropoxyphene	No Sr-89	2	0.26	1	0.13	2	0.26	0	0.00
	Sr-89	1	0.13	0	0.00	0	0.00	1	0.14

continued

TABLE 93 Number of patients taking analgesic medications by Sr-89 comparison (*continued*)

Analgesic	Treatment	Patients	%	On-study	%	Pre-CPFS	%	Post-CPFS	%
Dihydrocodeine	No Sr-89	26	3.43	12	1.59	22	2.91	5	0.72
	Sr-89	29	3.83	9	1.19	25	3.30	7	1.01
Fentanyl	No Sr-89	5	0.66	0	0.00	4	0.53	2	0.29
	Sr-89	4	0.53	0	0.00	2	0.26	2	0.29
Methadone	Sr-89	1	0.13	0	0.00	0	0.00	1	0.14
Morphine	No Sr-89	107	14.13	42	5.55	86	11.36	41	5.89
	Sr-89	105	13.87	44	5.81	83	10.96	44	6.32
Oxycodone	No Sr-89	37	4.89	9	1.19	23	3.04	18	2.59
	Sr-89	30	3.96	12	1.59	22	2.91	9	1.29
Tramadol	No Sr-89	51	6.74	21	2.77	43	5.68	7	1.01
	Sr-89	45	5.94	19	2.51	36	4.76	13	1.87
Buprenorphine	No Sr-89	1	0.13	0	0.00	1	0.13	0	0.00
	Sr-89	1	0.13	0	0.00	1	0.13	0	0.00
Fentanyl patch	No Sr-89	17	2.25	6	0.79	15	1.98	11	1.58
	Sr-89	14	1.85	3	0.40	10	1.32	7	1.01
Codeine paracetamol	No Sr-89	10	1.32	0	0.00	8	1.06	2	0.29
	Sr-89	6	0.79	1	0.13	3	0.40	2	0.29
Dihydrocodeine/ paracetamol	No Sr-89	3	0.40	0	0.00	2	0.26	1	0.14
	Sr-89	1	0.13	0	0.00	1	0.13	0	0.00

TABLE 94 Number of instances of analgesic medications by Sr-89 comparison

Analgesic	Treatment	Instances	OS	%	Pre-CPFS	%	Post-CPFS	%
Acetaminophen/ paracetamol	No Sr-89	5941	402	6.77	4503	75.80	1036	17.44
	Sr-89	6285	428	6.81	4777	76.01	1080	17.18
Aspirin	No Sr-89	125	13	10.40	93	74.40	19	15.20
	Sr-89	242	4	1.65	164	67.77	74	30.58
Diclofenac	No Sr-89	2306	176	7.63	1793	77.75	337	14.61
	Sr-89	2102	144	6.85	1640	78.02	317	15.08
Ibuprofen	No Sr-89	1255	76	6.06	1032	82.23	147	11.71
	Sr-89	1167	136	11.65	760	65.12	272	23.31
Naproxen	No Sr-89	487	38	7.80	397	81.52	52	10.68
	Sr-89	424	22	5.19	359	84.67	43	10.14
Codeine	No Sr-89	2470	157	6.36	1943	78.66	370	14.98
	Sr-89	2245	190	8.46	1726	76.88	329	14.65
Dihydrocodeine	No Sr-89	428	52	12.15	295	68.93	81	18.93
	Sr-89	446	34	7.62	362	81.17	50	11.21
Morphine	No Sr-89	4320	285	6.60	3141	72.71	893	20.67
	Sr-89	3999	222	5.55	2867	71.69	911	22.78
Oxycodone	No Sr-89	878	44	5.01	539	61.39	292	33.26
	Sr-89	1109	72	6.49	842	75.92	195	17.58
Tramadol	No Sr-89	738	84	11.38	598	81.03	56	7.59
	Sr-89	1220	83	6.80	932	76.39	205	16.80
Fentanyl patch	No Sr-89	546	36	6.59	349	63.92	160	29.30
	Sr-89	327	13	3.98	216	66.06	98	29.97

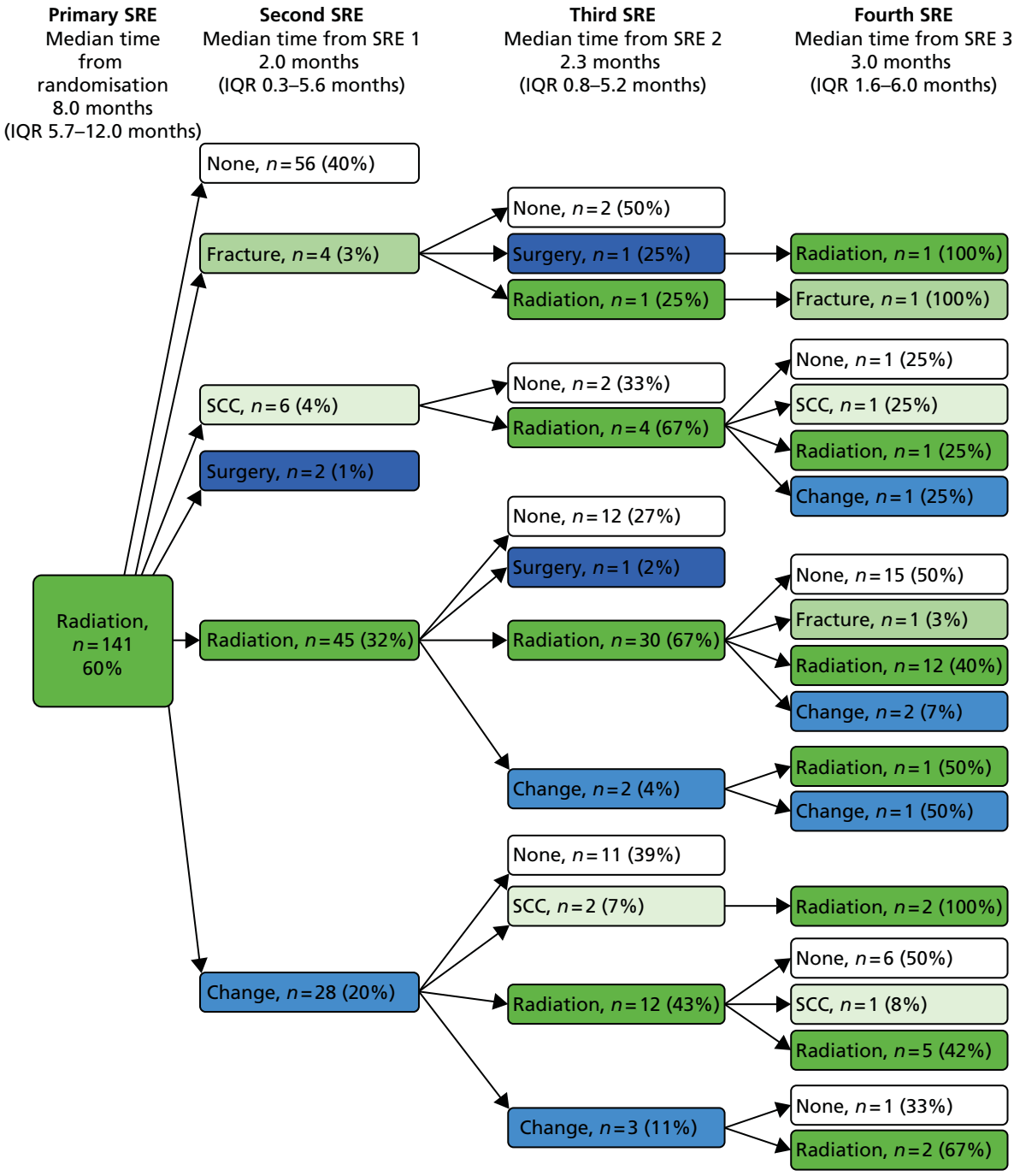


FIGURE 55 Depiction of time between SREs when first event was radiation: no ZA. Dark blue, surgery; mid-blue, change; dark green, radiation; mid-green, fracture; light green, SCC; white, none.

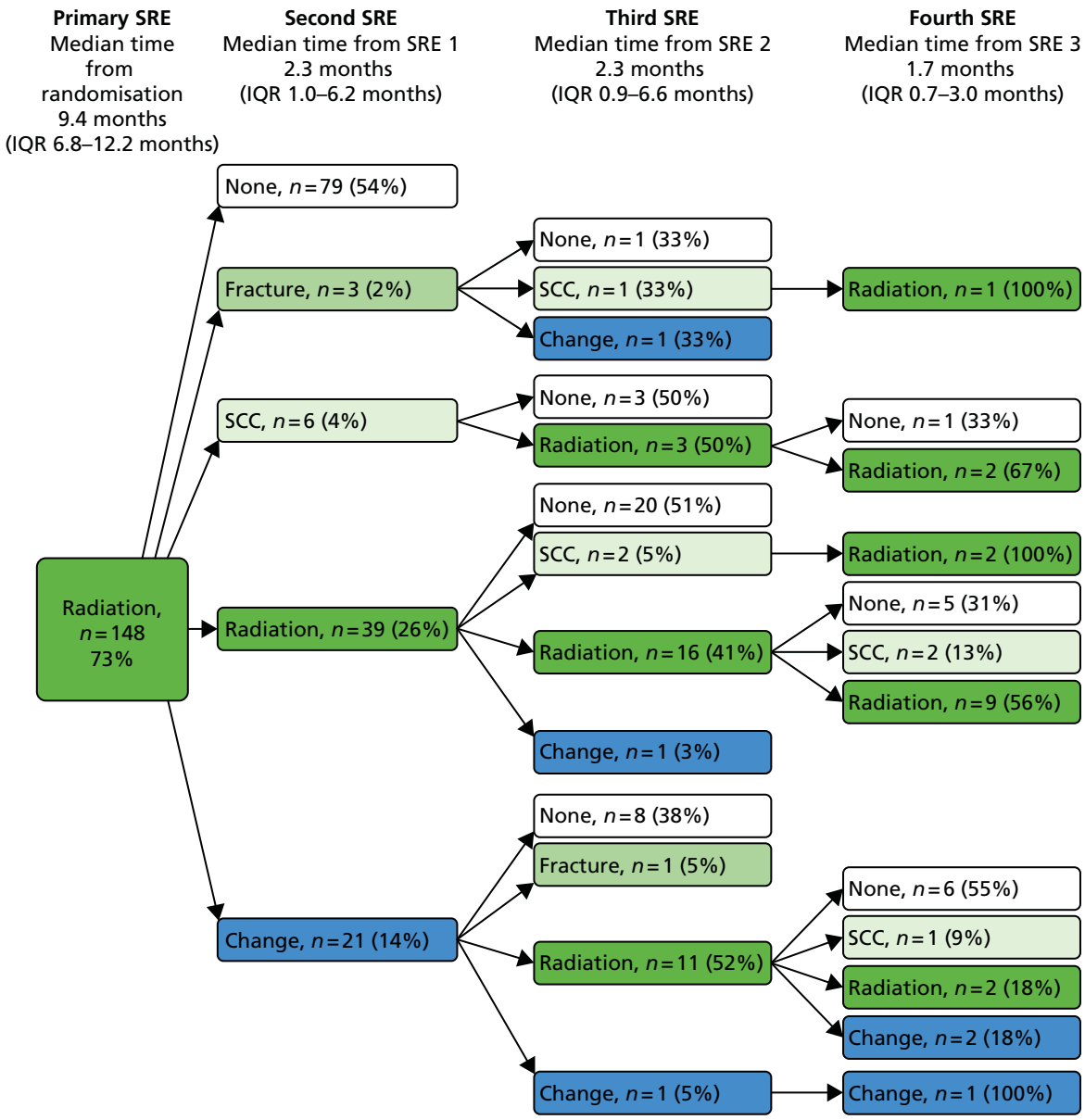


FIGURE 56 Depiction of time between SREs when first event was radiation: ZA. Mid-blue, change; dark green, radiation; mid-green, fracture; light green, SCC; white, none.

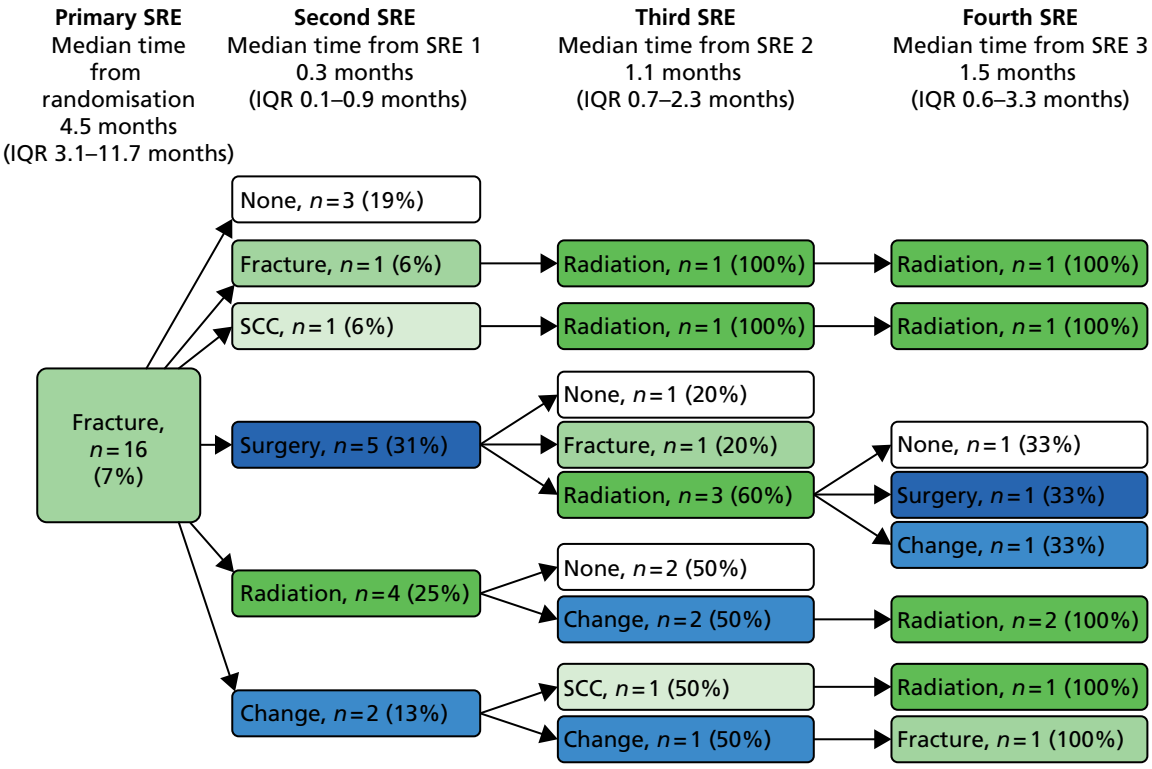


FIGURE 57 Depiction of time between SREs when first event was fracture: no ZA. Dark blue, surgery; mid-blue, change; dark green, radiation; mid-green, fracture; light green, SCC; white, none.

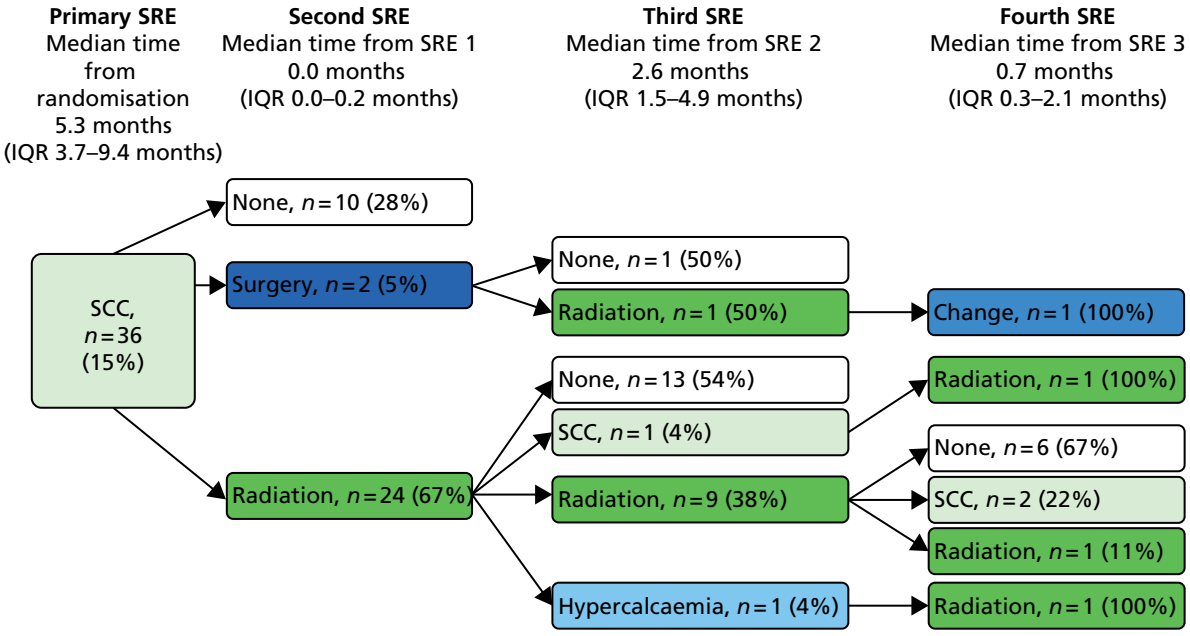


FIGURE 58 Depiction of time between SREs when first event was SCC: no ZA. Dark blue, surgery; mid-blue, change; light blue, hypercalcaemia; dark green, radiation; light green, SCC; white, none.

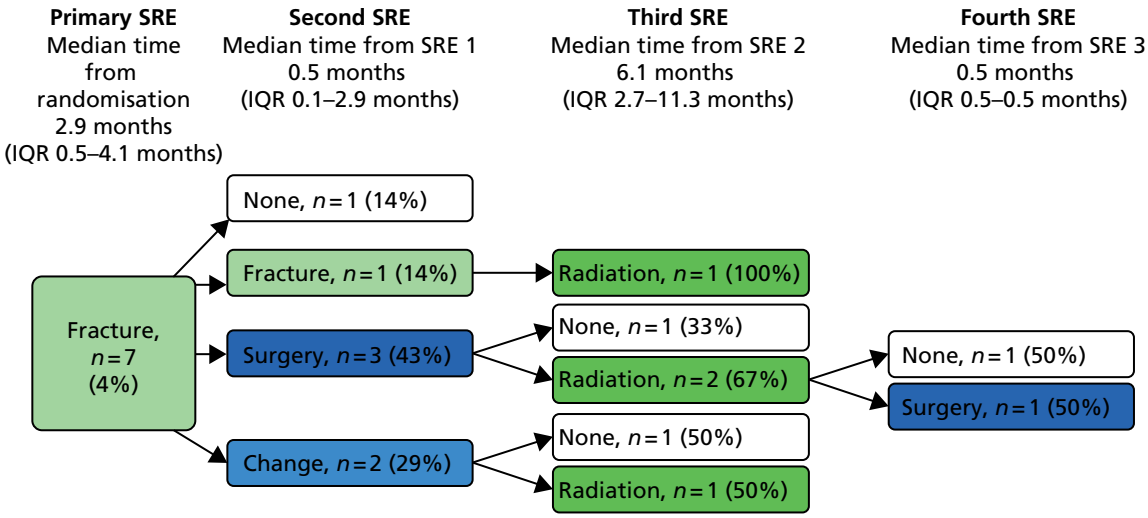


FIGURE 59 Depiction of time between SREs when first event was fracture: ZA. Dark blue, surgery; mid-blue, change; dark green, radiation; mid-green, fracture; white, none.

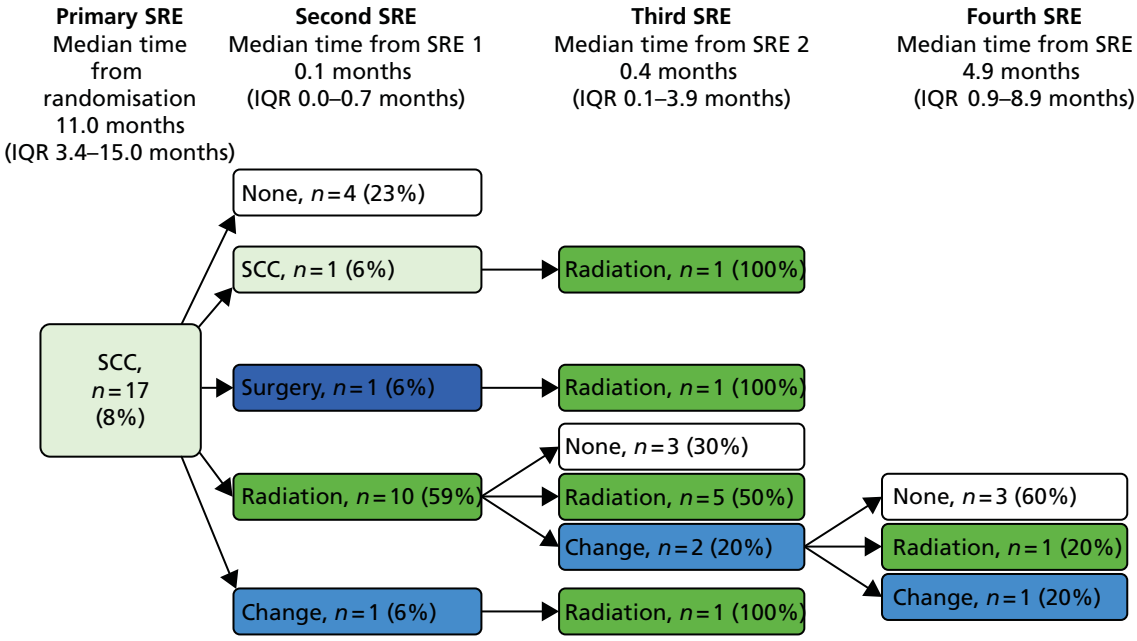


FIGURE 60 Depiction of time between SREs when first event was SCC: ZA. Dark blue, surgery; mid-blue, change; dark green, radiation; light green, SCC; white, none.

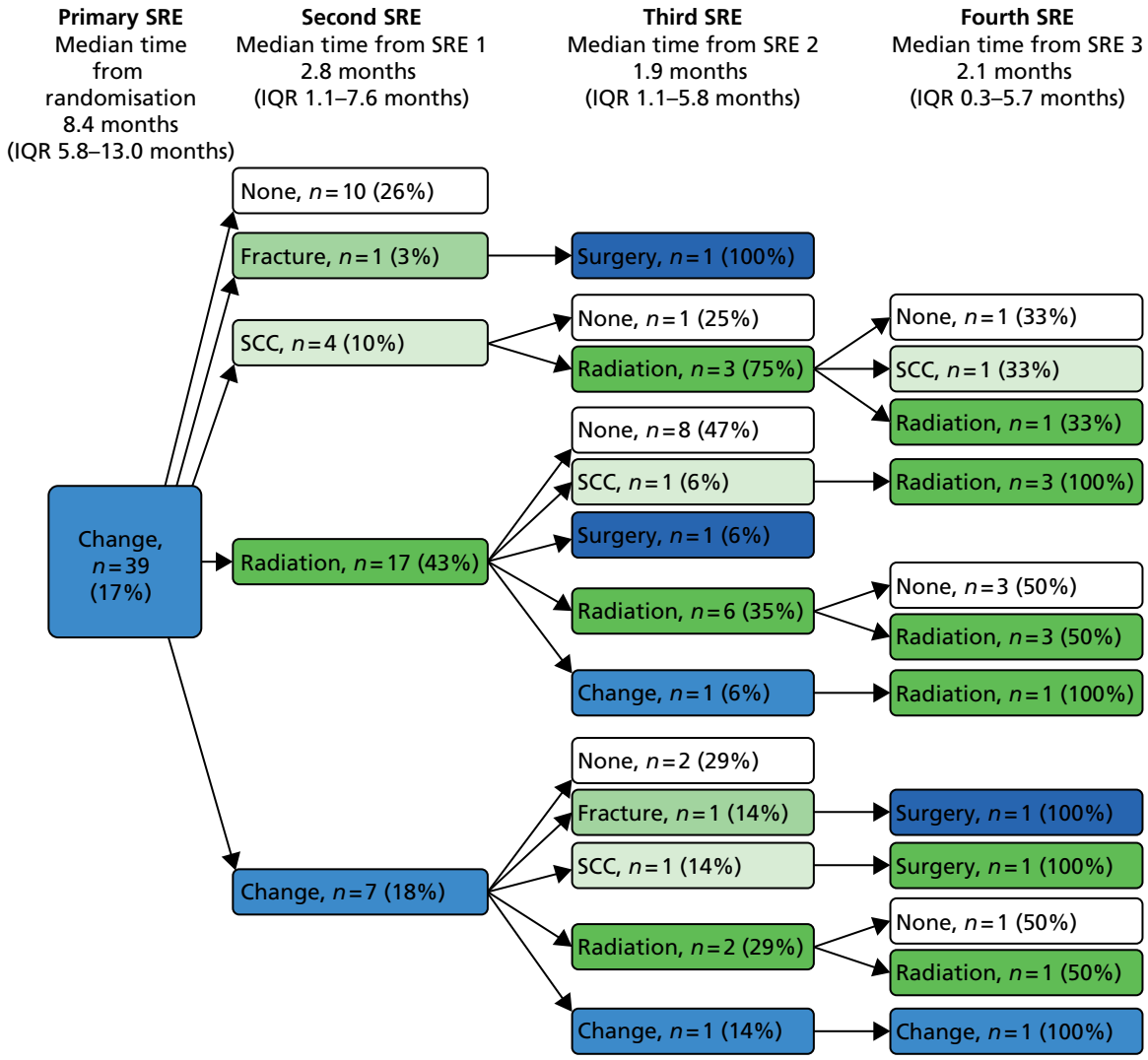


FIGURE 61 Depiction of time between SREs when first event was change in therapy: no ZA. Dark blue, surgery; mid-blue, change; dark green, radiation; mid-green, fracture; light green, SCC; white, none.

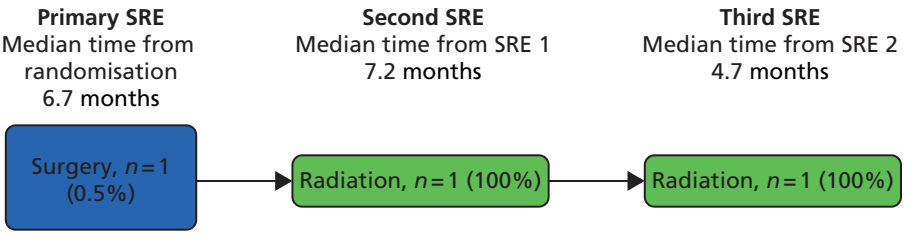


FIGURE 62 Depiction of time between SREs when first event was surgery: no ZA. Dark blue, surgery; dark green, radiation.

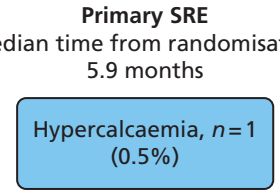


FIGURE 63 Depiction of time between SREs when first event was hypercalcaemia: no ZA. Light blue, hypercalcaemia.

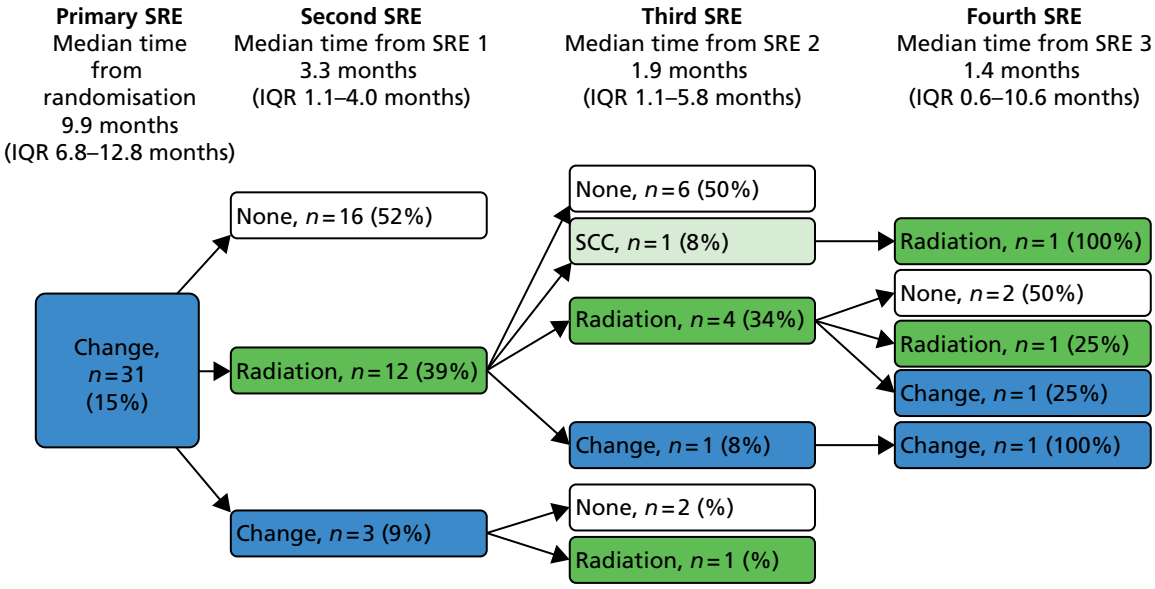


FIGURE 64 Depiction of time between SREs when first event was change in therapy: ZA. Mid-blue, change; dark green, radiation; light green, SCC; white, none.

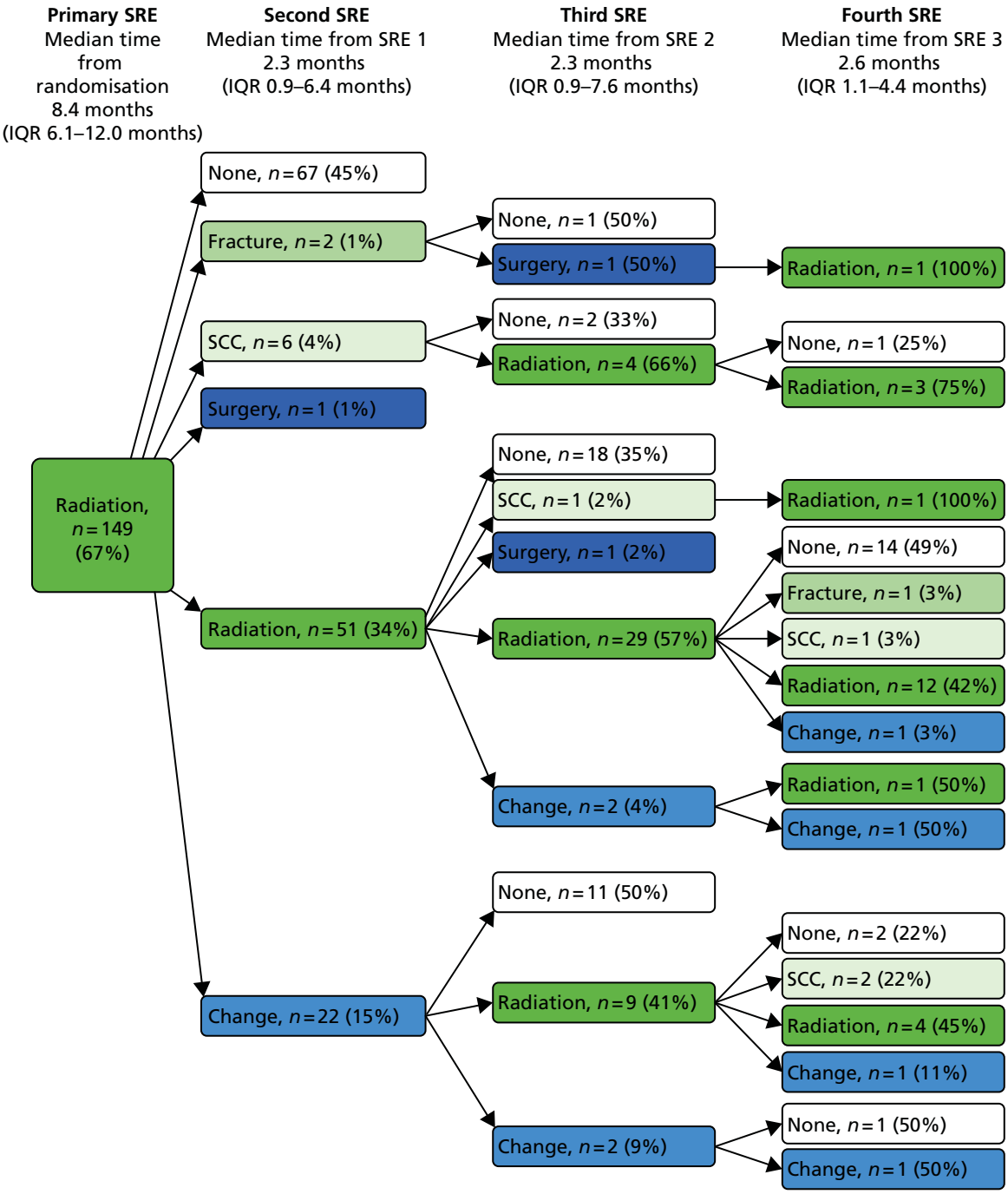


FIGURE 65 Depiction of time between SREs when first event was radiation: no Sr-89. Dark blue, surgery; mid-blue, change; dark green, radiation; mid-green, fracture; light green, SCC; white, none.

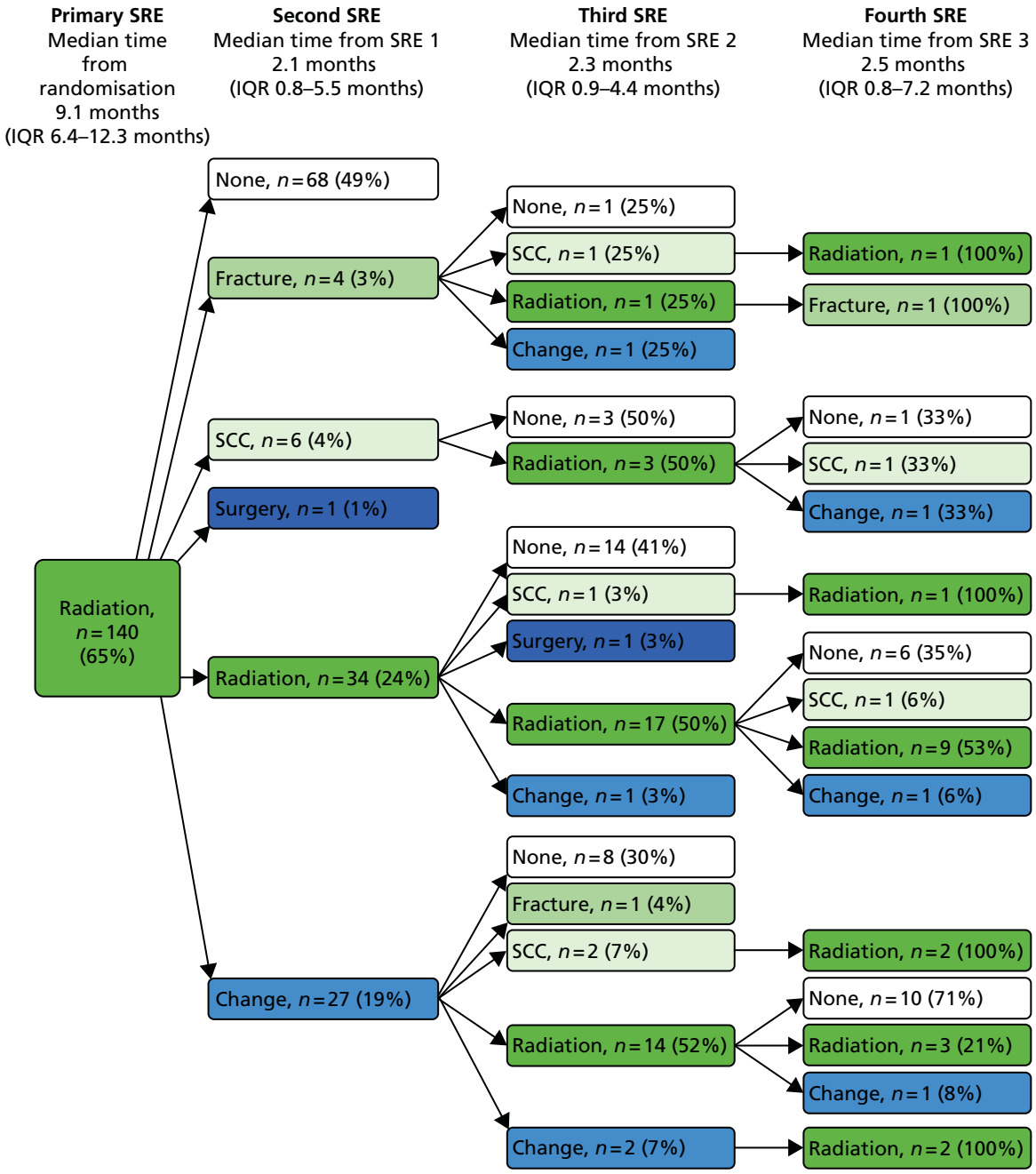


FIGURE 66 Depiction of time between SREs when first event was radiation: Sr-89. Dark blue, surgery; mid-blue, change; dark green, radiation; mid-green, fracture; light green, SCC; white, none.

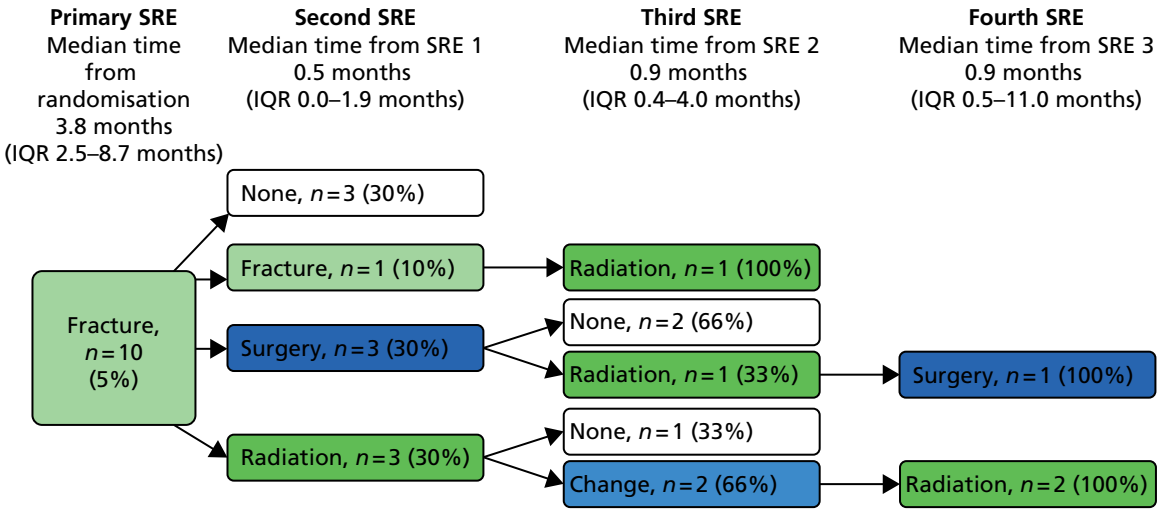


FIGURE 67 Depiction of time between SREs when first event was fracture: no Sr-89. Dark blue, surgery; mid-blue, change; dark green, radiation; mid-green, fracture; white, none.

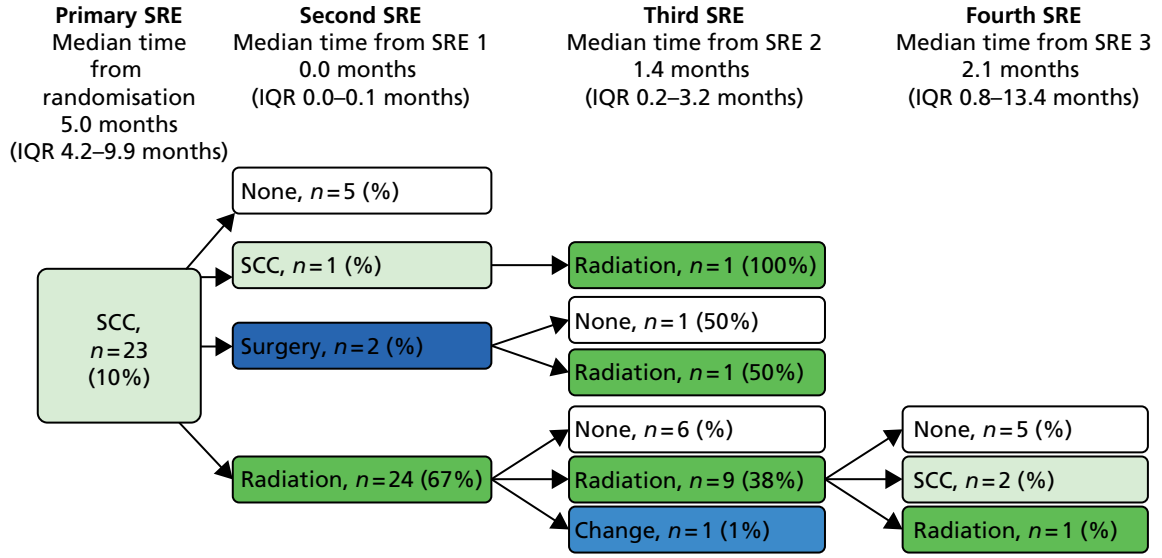


FIGURE 68 Depiction of time between SREs when first event was SCC: no Sr-89. Dark blue, surgery; mid-blue, change; dark green, radiation; light green, SCC; white, none.

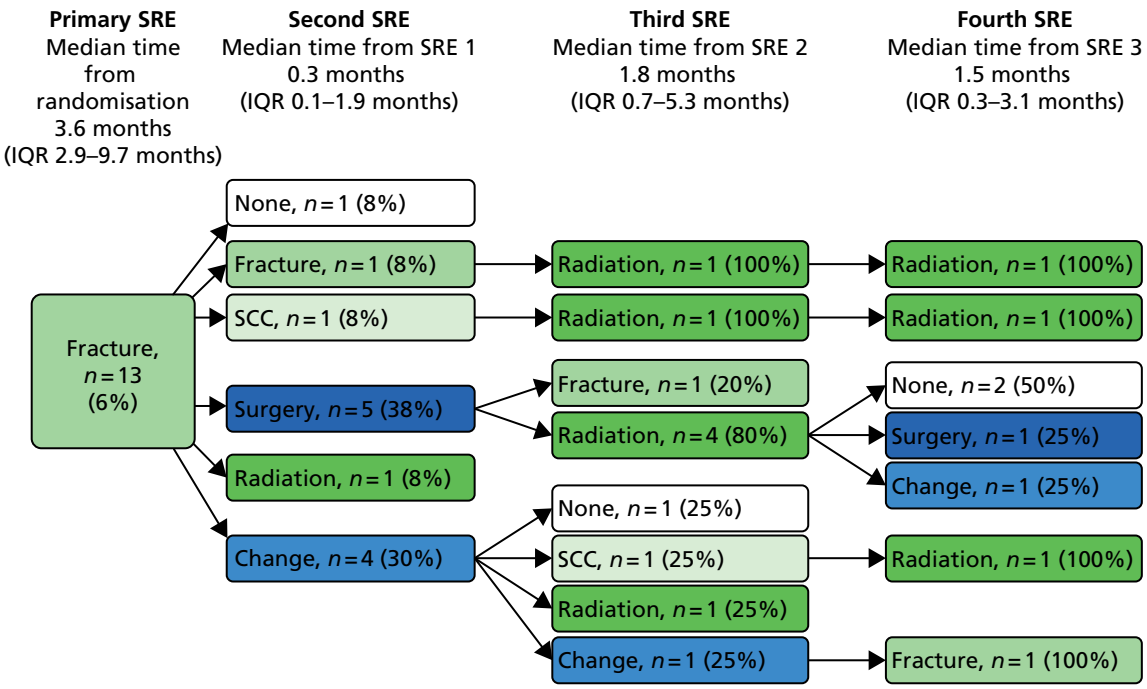


FIGURE 69 Depiction of time between SREs when first event was fracture: Sr-89. Dark blue, surgery; mid-blue, change; dark green, radiation; mid-green, fracture; light green, SCC; white, none.

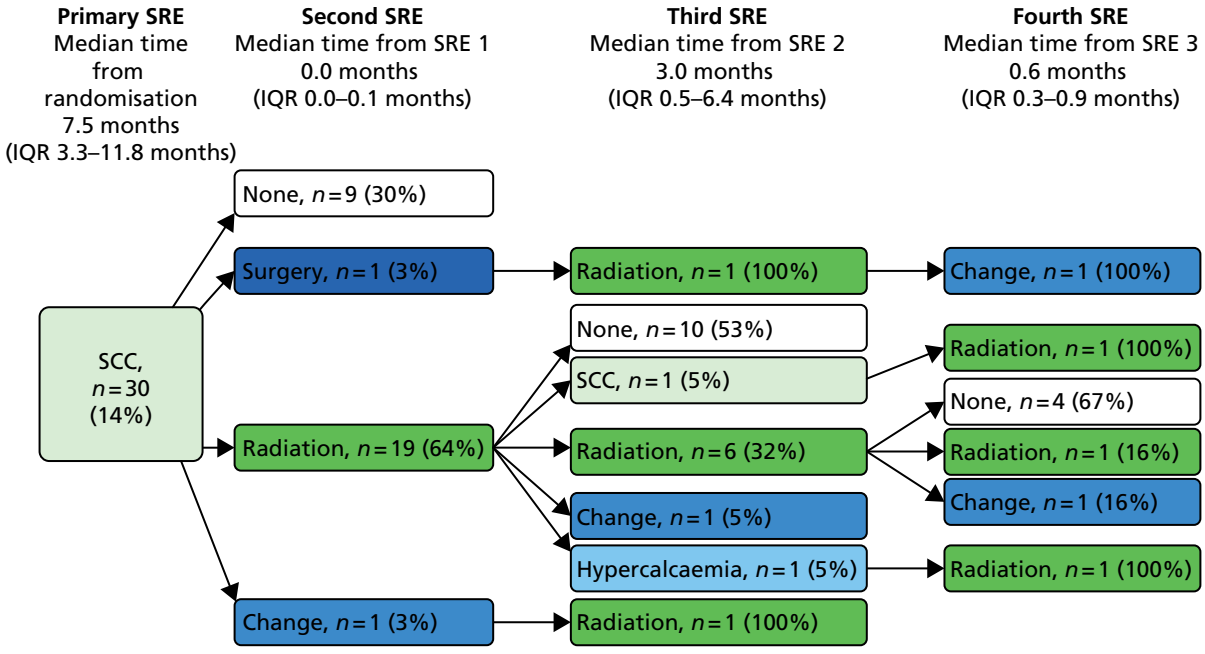


FIGURE 70 Depiction of time between SREs when first event was SCC: Sr-89. Dark blue, surgery; mid-blue, change; light blue, hypercalcaemia; dark green, radiation; light green, SCC; white, none.

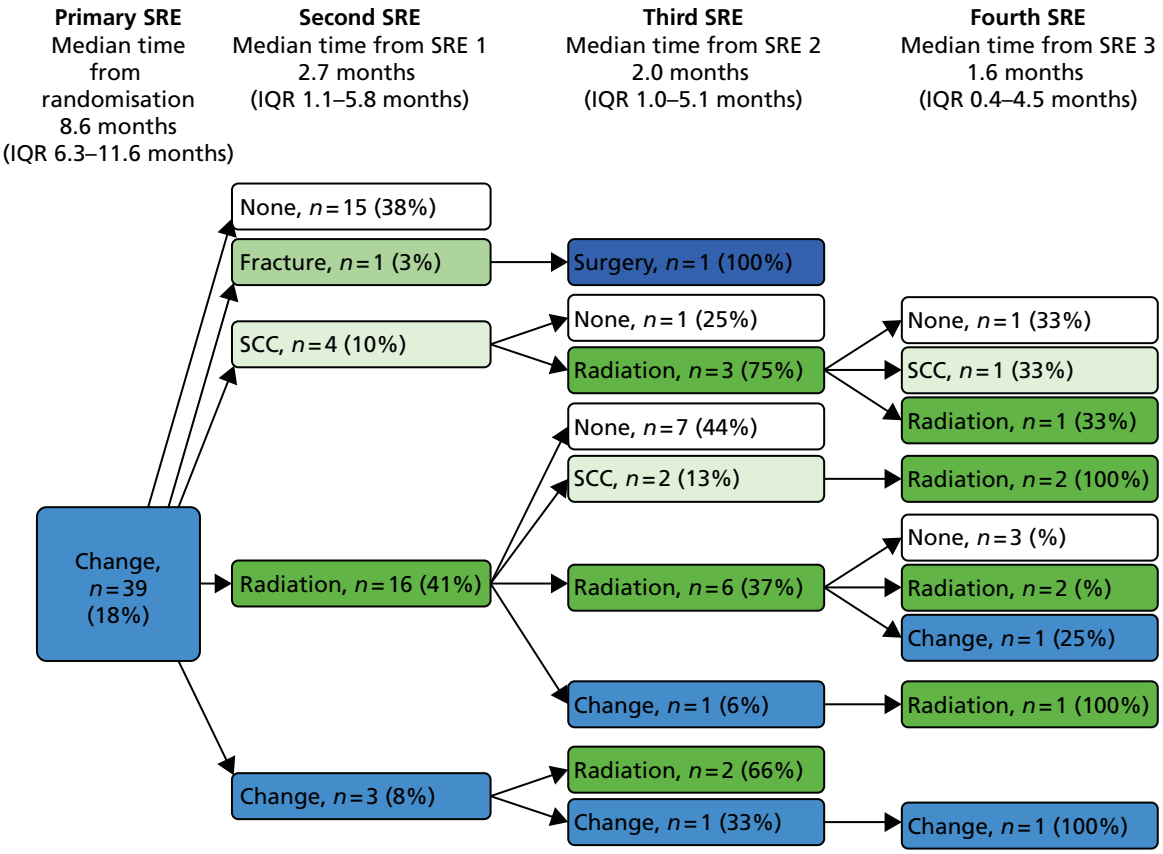


FIGURE 71 Depiction of time between SREs when first event was change in antineoplastic therapy: no Sr-89. Dark blue, surgery; mid-blue, change; dark green, radiation; mid-green, fracture; light green, SCC; white, none.

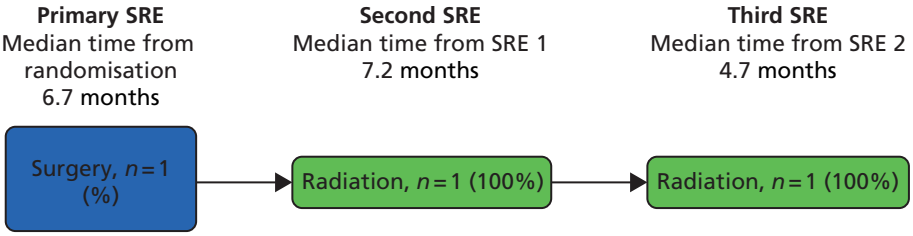


FIGURE 72 Depiction of time between SREs when first event was surgery: no Sr-89. Dark blue, surgery; dark green, radiation.

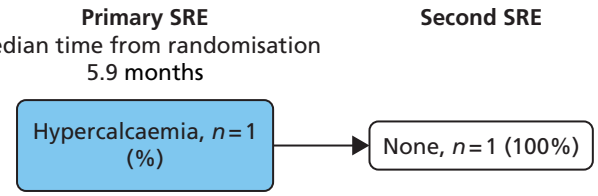


FIGURE 73 Depiction of time between SREs when first event was hypercalcaemia: Sr-89. Light blue, hypercalcaemia; white, none.

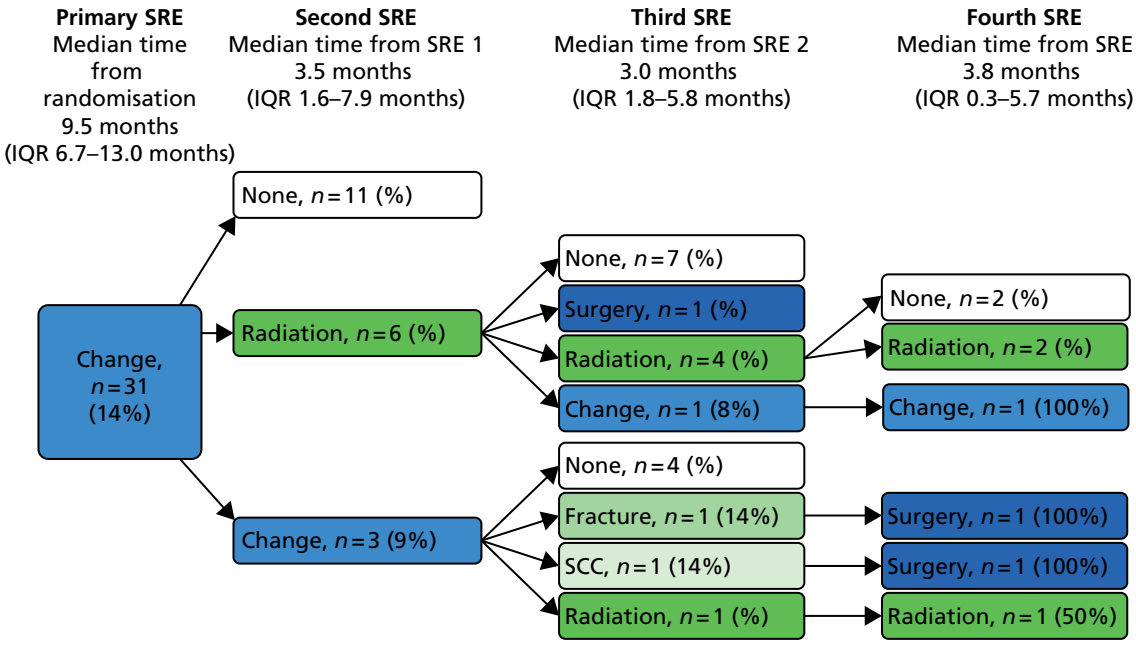


FIGURE 74 Depiction of time between SREs when first event was change in antineoplastic therapy: Sr-89. Dark blue, surgery; mid-blue, change; dark green, radiation; mid-green, fracture; light green, SCC; white, none.

Appendix 6 Resource use tables for economic evaluation

TABLE 95 Number (percentage) of people who received a treatment and average use for ZA and no ZA

Treatment/service	ZA			No ZA		
	n	%	Mean no. of cycles/units used	*n*	%	Mean no. of cycles/units used
Trial treatments						
Docetaxel + prednisolone	342	98	6.31	349	98	6.11
ZA	342	98	6.13	0	0	0.00
Sr-89	125	36	1.00	120	34	1.00
ZA as follow-up treatment	192	55	5.11	1	0	3.00
Concomitant medications						
Radiotherapy	177	51	1.65	204	57	1.95
Abiraterone	56	16	1.00	68	19	1.00
ZA as concomitant medication	73	21	3.77	63	18	1.94
Sr-89 as concomitant medication	15	4	1.00	21	6	1.00
Blood transfusion	31	9	2.10	22	6	2.50
Cabazitaxel	18	5	1.56	12	3	2.33
Docetaxel as concomitant medication	34	10	2.94	38	11	3.13
Mitoxantrone	23	7	2.30	15	4	1.87
Surgery	18	5	1.20	5	1	1.17
Outpatient appointments and inpatient stay						
Hospital outpatient appointment	296	85	5.79	293	82	5.25
Hospital inpatient stay	231	66	8.00	250	70	8.28
GP appointments	311	89	5.03	328	92	5.61

GP, general practitioner.

TABLE 96 Number (percentage) of people who received a treatment and average use for Sr-89 and no Sr-89

Treatment/service	Sr-89			No Sr-89		
	n	%	Mean no. of cycles/units used	*n*	%	Mean no. of cycles/units used
Trial treatments						
Docetaxel + prednisolone	345	99	6.23	346	97	6.19
ZA	172	49	6.14	170	48	6.12
Sr-89	245	70	1.00	0	0	0.00
ZA as follow-up treatment	90	26	5.10	103	29	5.10
Concomitant medications						
Radiotherapy	184	53	1.67	197	55	1.94
Abiraterone	59	17	1.00	65	18	1.00
ZA as concomitant medication	61	17	2.85	75	21	2.97
Sr-89 as concomitant medication	16	5	1.13	20	6	1.00
Blood transfusion	26	7	2.31	27	8	2.22
Cabazitaxel	19	5	1.84	11	3	1.91
Docetaxel as concomitant medication	36	10	3.11	36	10	2.97
Mitoxantrone	20	6	2.00	18	5	2.28
Surgery	13	4	1.23	10	3	1.10
Outpatient appointments and inpatient stay						
Hospital outpatient appointment	227	65	5.27	254	71	5.78
Hospital inpatient stay	295	84	8.52	294	82	7.80
GP appointments	311	89	5.10	328	92	5.55

GP, general practitioner.

TABLE 97 Number of instances of radiotherapy

Number of instances of radiotherapy	No ZA	ZA	Total
0	153	173	326
1	108	114	222
2	42	39	81
3	29	10	39
4	12	8	20
5	9	3	12
6	3	1	4
8	1	1	2
9	0	1	1

TABLE 98 Total number of instances of radiotherapy

Number of instances of radiotherapy	No ZA	ZA
Total number of instances of radiotherapy	398	292

TABLE 99 Number of instances of radiotherapy

Number of instances of radiotherapy	No Sr-89	Sr-89	Total
0	160	166	326
1	111	111	222
2	36	45	81
3	25	14	39
4	12	8	20
5	8	4	12
6	2	2	4
8	2	0	2
9	1	0	1

TABLE 100 Total number of instances of radiotherapy

Number of instances of radiotherapy	No Sr-89	Sr-89
Total number of instances of radiotherapy	383	307

TABLE 101 Average number of instances of radiotherapy: no ZA

Average number of instances of radiotherapy	No ZA	ZA
For patients who had radiotherapy	1.95	1.65
For all patients in the group	1.11	0.83

TABLE 102 Average number of instances of radiotherapy: no Sr-89

Average number of instances of radiotherapy	No Sr-89	Sr-89
For patients who had radiotherapy	1.94	1.67
For all patients in the group	1.07	0.88

EME
HS&DR
HTA
PGfAR
PHR

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